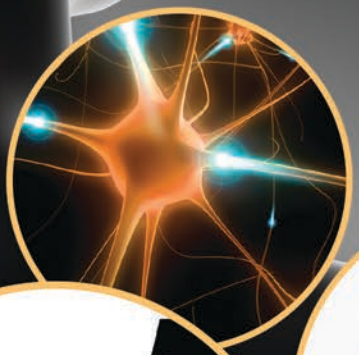
Fourth Edition

TRAUMATIC BRAIN INJURY

REHABILITATION, TREATMENT, AND CASE MANAGEMENT



EDITED BY
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Traumatic Brain Injury

Rehabilitation, Treatment, and Case Management, Fourth Edition

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Edited by
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Preface

In the late 1970s, the notion that an individual with an acquired brain injury could expect further recovery of function beyond 6 months postinjury was foreign. Treatment was predominantly rendered for long periods in inpatient rehabilitation facilities (IRFs) with long-term dispositions consisting of skilled nursing facilities, psychiatric hospitals, jail, the street, or home. Lengths of stay in IRFs could be protracted, ranging up to 6 months or longer. Hospital complications were common, and treatment often included strong psychotropic mediation, premature surgeries for oculomotor dysfunction and heterotopic ossification, grim prognostication, and minimalistic allied health involvement culminating in significant long-term disability.

As neuroscientists began to incorporate more intensive therapeutic interventions, recognition burgeoned that improvement was possible. Treatment techniques were borrowed from cerebral palsy, development disability, and stroke, and the treatment setting design became viewed as an ecologically important contributor to treatment outcomes. The brain was essentially a "black box" conundrum with the best information about its function arising from lesional observation and physiological studies that inferred function.

Now, neuroscience has matured at a remarkable pace, shedding far more exacting light on mechanisms of neurophysiology, pathophysiology of injury, neuroendocrinology, neuroimmunology, neuroplasticity, neuropharmacology, and neurodegenerative processes. Individuals with acquired brain injury are treated earlier and achieve far better recovery when financial support is available and uninterrupted. Sadly, we recognize that a chief determinant of whether an individual will receive rehabilitation services remains tied to socioeconomic status rather than a proscribed clinical pathway for treatment as is found in nearly all other aspects of medicine.

The fourth edition of this text constitutes a continuation of 20 years of coverage of traumatic brain injury and broadens the discussion of acquired brain injury. Within TBI, the paradigm shift from an injury occurring at a point in time to a disease entity of a chronic nature is changing the discussion of diagnosis, management, treatment, and outcome assessment. Disease specification that differentiates TBIs by the mechanism of injury, the exact nature of the injury, the extent of the injury, the presence of comorbidities and their exact nature, gender, age, race, and genome is emerging as crucial. There was a time when cancer was an undifferentiated disease. Disease differentiation has consequently impacted diagnosis, treatment, and outcome.

The intended legacy of this text has always been to provide comprehensive diagnostic and treatment guidance for professionals at all levels of practice and experience. Earlier editions focused on the role of medical and allied health professionals, case managers, legal professionals, and caregivers. This edition adds the role of the neuroscientist as an important provocateur of innovation in treatment and chronic disease management. It is no longer sufficient to simply treat a person to be able to eat, walk, and talk. We must push our field and all stakeholders to maximize recovery, minimize disability, and prevent or mitigate neurodegenerative processes that contribute to the pathogenesis and/or acceleration of neurological diseases. This text is intended to serve as a ready reference tool, contribute to professional growth of its reader, stimulate innovation and research, and promote continuing refinement of management of the diseases of acquired brain injury.

There is no other disease that so completely and suddenly renders competent people of all ages and walks of life vulnerable and unable to advocate for themselves. Of importance here is the recovery of the mind as well as the body. The disease destroys families, careers, and life aspirations. No other disease is referred to as "living death." No other disease requires the remarkable multitude of neuroscience, medical, allied health, case management, insurance, legal, religious, and social service professionals' involvement and coordination. The unprotected and neglected nature of life for injured individuals and their families after acquired brain injury commands our empathy, compassion, attention, and advocacy.

Acknowledgments

This text has been in continuous print for more than two decades, and the fourth edition promises to extend its run considerably. This endeavor has required the support of many.

First, I am tremendously grateful to Dr. David Hovda for coediting this edition with me. Dr. Hovda's vision for translating bench neuroscience lessons into potential clinical applications enabled the participation of many of this edition's contributors. It has been a highlight in my career to work with this fine scholar and remarkable gentleman.

Next, I am indebted to the many contributors contained herein and in previous editions. Their contributions have been timely and have served to educate many professionals. This edition could not have come about without the favors of both these authors and colleagues with whom I work. Their competence and willingness have provided all the time and resources necessary to both compile their contributions and make my own chapter preparations. Additionally, many of the illustrations were created by Craig and Betsy Persel for earlier editions and remain relevant today.

Of course, works like these invade family time. My wife, Sue, and my children, Matt, Jessica, Nick, Lindsay, and Ben, have been sure to keep me grounded and engaged in our wonderful family life and enjoying our seven beautiful grandchildren. They have been patient, supportive, and accommodating, sacrificing vacation time and accepting my distracted nature.

Mark J. Ashley, Sc.D., CCC-SLP, CCM, CBIST
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It is with great appreciation that I acknowledge all the authors that submitted chapters for our book, *Traumatic Brain Injury, Fourth Edition*. I especially wish to thank the number of basic scientists who made critical contributions and have given the reader a current status of plasticity and recovery as well as a glance at the future for potential recovery from this devastating injury.

I have had the pleasure of coauthoring and editing several texts over my career, and I must say I have thoroughly enjoyed my association with Dr. Mark Ashley, who truly was the mastermind behind this text. Had it not been for his dedication and enthusiasm for the topic, this fourth edition would not have come to the light of day. Consequently, on behalf of all of our students, faculty, researchers, clinicians, and current and future patients, I would like to thank each author who contributed chapters as well as Dr. Mark Ashley for making this remarkable text come to the forefront as it truly is a seminal contribution to the field.

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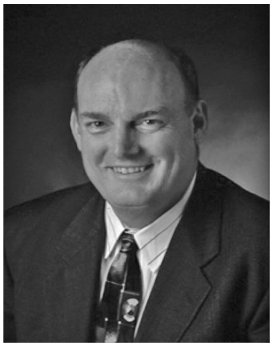
Dr. Mark J. Ashley is founder and president/CEO of Centre for Neuro Skills (CNS), which has operated postacute brain injury rehabilitation programs in Bakersfield, Los Angeles, Dallas, Fort Worth, and San Francisco since 1980. In 2011, Dr. Ashley participated in the Blue Ribbon Panel on Traumatic Brain Injury and Post-Traumatic Stress convened by Generals Peter W. Chiarelli and Joseph Dunford, and he established the CNS Clinical Research and Education Foundation, a nonprofit research organization. He serves on the board of directors of the Brain Injury Association of America (BIAA) and holds several positions in that organization, including chairman emeritus, chair of the fund development committee, and member of the Business and Professional Council. Dr. Ashley also serves on the board of directors of the California Brain Injury Association and is chairman emeritus. He is an adjunct professor at the Rehabilitation Institute of the College of Education at Southern Illinois University and a member of the advisory board of the Center for Applied Neuroscience, University of Cyprus. Dr. Ashley received his master's degree in speech pathology and a doctorate of science from Southern Illinois University in Carbondale, Illinois. He is a licensed speech-language pathologist in California and Texas and is a certified case manager.



Dr. David A. Hovda is the director of the UCLA Brain Injury Research Center, which was created in 1990. It incorporates teaching, research, patient care, and service for patients suffering from traumatic brain injury. Dr. Hovda has received a number of awards for his research on brain injury and recovery of function, including the "Strength of the Nation Award" from the United States Army in 2011. This is the highest civilian award given by the Secretary of the Army in recognition of Dr. Hovda's efforts to help treat military personnel suffering from mild traumatic brain injury returning from theater. In addition, Dr. Hovda received the Alumni Association's James F. Zimmerman Award from the University of New Mexico in 2012 for his research accomplishments recognized in the field of traumatic brain injury. Dr. Hovda is most well known internationally for his translational work on the pathobiology of traumatic brain injury and has devoted most of his career to understanding the mechanisms of recovery of function. Dr. Hovda continues to serve as a consultant for professional sport organizations as well as the Department of Defense, addressing issues related to traumatic brain injury and recovery of function. Dr. Hovda is a professor of neurosurgery and of molecular and medical pharmacology at the David Geffen School of Medicine at UCLA. He received his doctoral degree under the supervision of Dr. Dennis M. Feeney in the field of Physiological Psychology at the University of New Mexico. He completed his postdoctoral training in neurophysiology under Dr. Jamie Villablanca at UCLA.

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PART 1

Neuroscience

1

Bioscience indications for chronic disease management and neuromedical interventions following traumatic brain injury

MARK J. ASHLEY, GRACE S. GRIESBACH, DAVID L. RIPLEY, AND MATTHEW J. ASHLEY

INTRODUCTION

Rehabilitation for acquired brain injury (ABI) has focused largely on alleviation of physical, cognitive, communicative, neurobehavioral, and psychological deficits arising from the injury. Recently, ABI has come to be viewed as a chronic disease and, more probably, a collection of various diseases. Increasingly, there is concern that brain injury may contribute to the pathogenesis of neurodegenerative conditions as well as to acceleration of what may be genetically predisposed neurological diseases.[1–15] Traumatic brain injury (TBI) is implicated in epilepsy, stroke, brain cancer, multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD), and Alzheimer's disease (AD). Further, hypothalamic and pituitary damage can result in a wide variety of neuroendocrine disorders.[16–21]

The pathophysiology of TBI includes neurodegenerative components, the temporal end points of which are unclear.[22] Injury to the brain includes not only physical damage to structures, but also disruption of normal physiological processes and disruption of the blood–brain barrier (BBB).[23–27] We must consider the possibility that the injured brain is no longer properly segregated from the periphery and inflammatory developments within the periphery. Inflammatory processes that accompany brain injury also impact the BBB and can reactivate long after an initial insult to the brain.[28–30]

Rehabilitation following ABI has, thus far, focused little on neurophysiologic function as a basis for chronic intervention. Currently, most pharmacological intervention during rehabilitation addresses symptoms for epilepsy, depression, agitation, sleep, cognition, or motor function.

Medical stability and functional outcome are dependent on multiple pathophysiological processes beyond metabolic alterations. This chapter addresses multiple factors that have an influence on neuroinflammatory and neurodegenerative processes after ABI. It is important to consider different pathophysiological processes because they may contribute to improving the extent and/or rate of recovery following ABI. Further, these factors appear to be important in that they may inhibit maximal recovery or contribute to pathogenesis and/or progression of neurodegenerative diseases. Development of more thoughtful subacute, postacute, and chronic medical management approaches for ABI is necessary with an eye toward furthering disability reduction, optimizing neurophysiologic function post-ABI, preventing

disease causation, and/or mitigating disease progression. The limited regenerative capability of the brain suggests that any additional loss of structures following ABI may have widespread implication throughout the body.[31]

LOSS OF AXONAL INTEGRITY AFTER TBI

Structural changes associated with acute and chronic TBI logically serve as a basis for recovery and potential aging-related conditions. It is important to appreciate the pathophysiologic complexity and heterogeneity of TBI. As such, consideration of the nature and type of injury to neural structures may be important to consider. Depending on the biomechanical insult to the brain, TBI can have predominantly focal or diffuse effects. The initial damage has metabolic consequences that can be exacerbated by secondary insults, such as hypoxic/ischemic events. All this is likely to contribute traumatic axonal damage.[32]

Focal damage can be expected to impact certain motor, sensory, or cognitive functions, depending upon the neural structures or systems involved. Diffuse axonal injury (DAI) is recognized as a primary component of neurophysiological dysfunction in 40% to 50% of all brain injury of traumatic etiology.[33] DAI tends to affect specific regions of the human brain, such as the parasagittal white matter of the cerebral cortex, the corpus callosum, and the pontine–mesencephalic junction adjacent to the superior cerebellar peduncles.[34] At the cellular level, direct forces of sufficient magnitude breach the cellular membrane, initiating a cytotoxic, biochemical cascade of events, which impacts neuronal health and function in the immediate vicinity of the primary damage (Figure 1.1).[35] The damage inflicted by this cytotoxic biochemical cascade, however, may not be restricted to the locality of the primary site of damage and may reach far distant cellular structures within the central nervous system (CNS).[36]

More specifically, axolemmal permeability is induced by trauma, resulting in a local influx of Ca^{2+}. Cysteine proteases, such as caspases and calpains, participate in cytoskeletal membrane degradation that occurs over time.[22] One of these cleaved proteins is spectrin. Spectrin is a major constituent of the cytoskeletal membrane. Moreover, increases in calpain lead to mitochondrial injury that result in the release of cytochrome-C and caspase activation.

Neurofilaments are a major component in the neuronal cytoskeleton. Neurofilamentary changes compromising structural support will occur in a subset of severe TBI and are likely to contribute to the mechanical failure of the axonal cytoskeleton.[37] In turn, loss of axonal integrity impacts protein transport and mitochondrial migration. Mitochondria are transported from their site of biosynthesis in the cell body to positions along the axon or terminal.[38–41]

One of the mechanisms that can lead to axonal loss after injury is Wallerian degeneration. This type of degeneration is observed when the axon is transected and portions distal to the injury site deteriorate. Neurofilamentary changes associated with Wallerian degeneration, however, are not immediate. Wallerian-type axonal degeneration progresses from axonal swelling, compromising axonal integrity and facilitating its rupture. This degradation will lead the axon to draw back toward the cell body and form an axonal bulb. Axonal degeneration is followed by infiltration of macrophages that can be observed as small clusters of microglia.[42] At a cellular level, this includes residual endogenous brain peptides and small proteins,[43] immunoreactive astrocytes in injured areas,[44,45] beta-amyloid protein deposition,[46] and neurofibrillary tangles.[47] These changes occur from days to months to years after injury. Active myelin degeneration occurs as the final stage in the neurodegenerative process in the first 2 years after DAI.[48]

DAI relates to axons that are lost to either apoptosis or necrosis. Other axons, however, can be reparably injured (traumatic axonal injury, TAI). Disruption of microtubule

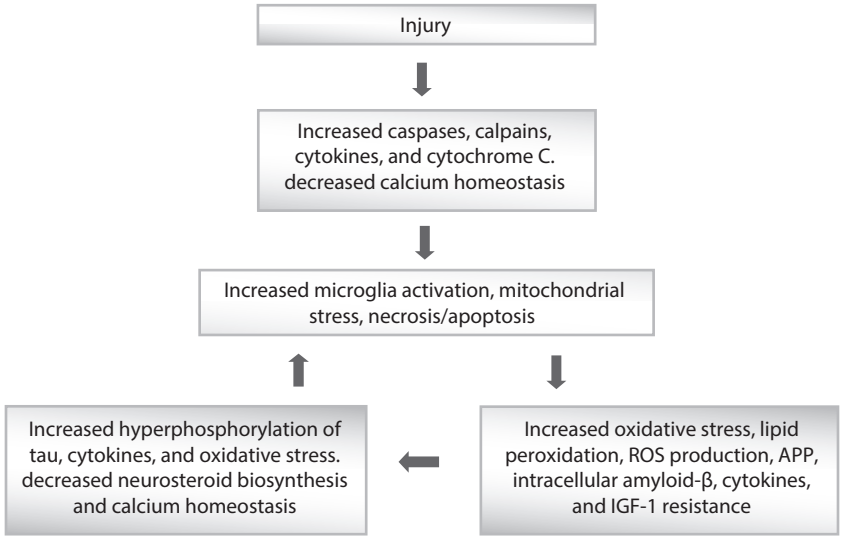

Figure 1.1 Summary of neurodegenerative events.

structures via stretching or deformation appears recoverable in some cells. In these cells, axonal transport is reversed, averting accumulation of transported proteins and organelles, enabling the cell to recover rather than succumb.[22] Tau protein, a microtubule-associated protein (MAP), serves to stabilize microtubule transport assemblies within the axon and, once destabilized, contributes to dysfunction of microtubules and destabilization of the cytoskeletal network. Tau protein is implicated in inflammation-dependent pathways subsequent to brain injury vis-à-vis its hyperphosphorylation.

BLOOD–BRAIN BARRIER

The BBB is a multicellular structure that segregates the CNS from the blood flow of the periphery. While separating the brain from peripheral circulation, the BBB enables the delivery of oxygen and nutrients to cells in the CNS. It participates in the elimination of toxins from the CNS and protects the CNS from pathogens in the periphery. The BBB along with a number of interdependent structures, such as astrocytes, microglia, and pericytes, is often referred to as the neurovascular unit (NVU). The failure of any one of its interdependent structures can result in BBB disruption.[49] In turn, the integrity of the BBB is crucial for proper neuronal function.

The NVU is comprised of the cerebral vessel itself, formed by endothelial cells, tight junctions, adherens junctions, peg–socket junctions, the pericyte, basement membrane, astrocytes, microglia, and neurons.[49] The NVU functions to control the influx of molecules and ions to the brain from the blood and efflux from the brain to the body in what is referred to as transcytosis. Transcytosis is very slow in the BBB in contrast to rates in other tissues. Molecular transport across the BBB is dependent upon specific transporters, and molecular size while protection of incursion of immune cells into the CNS is brought about by low expression of leukocyte adhesion molecules in endothelial cells.[50] The BBB enables these effector responses to brain infections and also enables clearance of debris after brain tissue damage by macrophages.[50,51]

Although the BBB functions at all levels of the arterial and venous supply, some specialization exists. For example, capillaries in close proximity to neurons provide for nutrient transport while leukocyte management and immune modulation occurs at the level of the postcapillary venule.[52,53]

Astrocytes in the NVU regulate the BBB and provide for transport of nutrients to neurons. Astrocytes regulate extracellular potassium balance and manage neurotransmitter clearance and recycling.[54] Cholesterol and the phospholipid transporter molecule apolipoprotein E (APOE) are produced by astrocytes mediating brain homeostasis-regulating processes.[54] Astrocytes also modulate the BBB's tight junctions by secreting sonic hedgehog (SHH) and angiotensinogen.[55,56] SHH plays a key role in brain development and cell division. The endothelial cells express hedgehog receptors (Hh) and thus, SHH and Hh promote BBB development and integrity. In addition, the Hh pathway decreases expression of proinflammatory mediators and adhesion and migration of leukocytes, thereby promoting CNS immune quiescence.[56]

BBB integrity is also mediated by APOE2 and APOE3 alleles with APOE3 being in highest concentration in humans.[57,58] In contrast to APOE2 and APOE3, APOE4 promotes disruption of the BBB by activating an inflammatory and tight junction disruptive pathway in pericytes.[59] APOE2 and APOE3 suppress this same pathway.[59]

The BBB is disrupted by injury to the CNS, including TBI.[23, 25, 27, 60–62] Although influx in the BBB repairs relatively well in juvenile animals after trauma, efflux may fail to properly repair, resulting in accumulation of toxins, such as reactive oxygen species (ROS), amyloid β, and other mitochondrial toxins behind the BBB.[23] Oxidative stress resulting in an excess of ROS mediates BBB breakdown, which, in turn, facilitates neuroinflammatory responses. These responses are also implicated in ischemic stroke, epilepsy, ALS, and MS.[63–65] These same conditions have been linked to prior TBI, suggesting that perhaps chronic reinitiation of BBB breakdown is a plausible pathogenic contributor.

Evidence exists for the presence of chronic perivascular iron deposition (siderosis) associated with previous perivascular hemorrhage in cortical, subcortical, brainstem, and cerebellar structures.[66] Primary areas of involvement include the parasagittal white matter, the corpus callosum, the internal capsule, and the deep gray matter. The presence of hemoglobin-derived iron can induce formation of ROS, causing microglia and astrocytes to become activated and initiating a neuroinflammatory response.[62] This is the basis for motor neuron degeneration seen in ALS.

MICROGLIA

Disabilities frequently persist beyond the first weeks following a TBI. The pathological substrate behind these disabilities is most likely due to both the effects of the initial biomechanical insult, i.e., primary damage, and secondary damage resulting from extracranial and intracranial events. Pathological mechanisms initiated by TBI continue months after the initial insult and are likely to contribute to long-lasting neurodegeneration.[28,67–70] Here, we discuss how persistent inflammation can lead to chronic neurodegeneration.

Cerebral inflammation is mediated by microglia

Inflammation in the brain is typified by microglial activation and the expression of key inflammatory mediators. Microglia are part of the glial family of non-neuronal cells that mediate immune responses in the CNS. They are the resident macrophages in the CNS given their capability to engulf particles. Microglia mediate responses to pathogens and/or injury and provide support, synaptic pruning, and immunological activities within the CNS.[71] Microglia routinely remove live glioma cells when activated.[72] Microglia

are constantly surveying the environment by interacting with both neurons and glia.[73] Thus, their responses are dependent on their surrounding environment. One of these microglial responses is the capability to transform from a resting state to an alert and reactive state. This microglial switch occurs when the concentration of particular molecules increases, the exact nature of which requires further study. This implies that microglial activation is responsive to the level of tissue damage. Accordingly, microglial responses are linked to alterations in BBB permeability. As indicated above, the BBB is comprised of a vascular endothelium and a blood cerebrospinal fluid barrier that control the passage of soluble factors from circulating blood to the brain.[74] Given that the BBB helps maintain the necessary environment for proper neuronal circuit function, any perturbations in its permeability are likely to lead to microglial activation.

Activated microglia will facilitate increases in markers of inflammation as well as inflammatory mediators, such as histocompatibility complex, CD68, and NADPH oxidase. When microglia become "activated," they produce inflammatory cytokines. These are small proteins that allow for immune response signaling. Microglia also undergo structural changes through cytoskeletal rearrangement, altering the pattern of receptor expression and facilitating cytokine communication between cells and enabling migration toward sites of injury or infection.[75]

Major proinflammatory cytokines are interleukins (IL), interferon-γ (IFN-γ), and tumor necrosis factor (TNF). These cytokines interact with microglia via surface receptors and adhesion molecules and will modulate destructive processes, such as microglial phagocytic performance. These destructive processes will, in turn, lead to the recruitment of more microglia.[76] Cytokines also control microglial motility, enabling microglia to migrate to a site of injury following signals of already activated microglia.

The phagocytic line of defense not only diminishes the menace presented by particular particles, but it can remove dead and damaged neurons that can compromise regional signaling.[77] Damaged or stressed cells emit signals that are indicative of their deteriorating state.[78] These signals, also known as "eat me" signals, are detected by the surrounding microglia.[79] It should be noted that "eat me" signaling can be reversed in stressed but viable neurons.[78]

When addressing differential states of microglial activation, it is not uncommon to note that terminology used to describe macrophage activation (M1/M2) has been adopted. Under this terminology, microglia under an M1 state is associated with a defensive proinflammatory reaction. Thus, inflammatory cytokine production by microglia occurs in M1 activation. In contrast, microglia under an M2 "resting state" is associated with an anti-inflammatory response leading to homeostasis.[80,81] Nevertheless, although microglia is functionally quiescent during the resting state, it is still monitoring the environment through its receptors.[79,82]

Microglial alterations following TBI

Following either focal or diffuse TBI, microglial upregulation occurs and can be long lasting.[28,70,83] Disruptions in BBB integrity play a critical role in the initial neuroinflammatory response. BBB integrity may be compromised by TBI.[84] Permeability of the BBB will allow for increased cytokine infiltration to the brain. In turn, increases in cytokine levels will lead to the induction of other cytokines,[85] thus ultimately heightening microglial activation. In addition, when the BBB is leaky, proteins and water will contribute to vasogenic edema that, in turn, exacerbates the cytotoxic edema, i.e., cellular swelling, that may already be taking place. Accordingly, microglial activation is prominent at the more focal injury sites during the acute period.[86]

Increased immune activity can be observed years after the initial injury. Postmortem studies show chronic microglial upregulation in the corpus callosum and frontal lobes of humans months to years postinjury.[28,69,87] This is in accordance with animal studies showing prolonged microglial activity after TBI.[68,88] Similarly, lasting increases in microglial activation after TBI have been reported in a human study utilizing positron emission tomography. This study found that activation was most notable in subcortical and cortical regions with apparently undamaged tissue. In contrast, persistent microglial activation was not significantly observed in regions with pronounced tissue damage.[30] It is likely that the formation of glial scarring isolating the damaged area could have impeded microglial activation.[89]

Microglia can also switch into an intermediate alert or primed state after TBI. Microglial inflammation after TBI has been observed to resolve within 72 hours in mice, although a priming effect of an initial traumatic injury is also evidenced at 1 month postinjury with exaggerated expression of proinflammatory cytokines.[83] In an alert or primed state, the threshold to switch to an activated state is lowered, therefore potentially leading to an exaggerated inflammatory response when presented with an immune challenge.[90] In this instance, microglia become activated in response to infection in the periphery where they would not normally. This phenomenon has been described in aging and, notably, also after TBI.[91,92] Experimental TBI studies have indicated that microglia present a primed state during the postacute period accompanied by an exaggerated expression of proinflammatory cytokines associated with neurodegeneration when presented with an immune challenge. This was observed by increased IL-1β and TNF-α following a lipopolysaccharide challenge.[83] Microglial activation response is exaggerated to secondary or subthreshold stimuli. The consequence can be substantial changes in plasticity, development or worsening of cognitive deficits, and acceleration of neurodegeneration.[91] Indeed, amplified microglial responses can negatively affect behavioral processes[93] and may contribute to the prevalence of affective and cognitive impairments after TBI.[94,95] Accordingly, a secondary immune challenge is known to exacerbate cognitive impairments in those that are already presenting cognitive

decline.[96,97] A potential mechanism contributing to the exacerbation of cognitive and affective impairments following an immune challenge after TBI can be the interaction of cytokine infiltration from the periphery with primed microglial responses found after injury.

Increases in cytokines are associated with sickness behavior that is manifested as fatigue, decreased appetite, hyperalgesia (i.e., increased sensitivity to pain), impaired concentration, depression, and sleep disturbance.[98,99] Interestingly, the above symptoms, which are prevalent during infection, are also commonly observed with depression and TBI. Moreover, cytokines appear to contribute to the occurrence of depression by stimulating the hypothalamic–pituitary axis[100] and affecting the metabolism of monoamines, such as serotonin and norepinephrine.[101–103] Accordingly, increases in cytokine production have been associated with depression.[104,105]

Neuronal activation of brain regions responsive to stress is associated with microglial activation. These brain regions include the amygdala, prefrontal cortex, and regions within the hippocampus.[106–110] The association between microglial activation and the abovementioned regions is apparent during periods of chronic stress because microglia mediate neuronal adaptation after stress.[111] This is particularly concerning after TBI when a heightening of the stress response has been observed [112] and may interfere with experience-dependent plasticity.[113] This is in accordance with the high prevalence of immune dysfunction in those suffering from mood disorders[114,115] and includes those that suffered a TBI.

Inflammation and axonal damage

As indicated above, prolonged neuroinflammation and microglial activation result from chronic biochemical processes initiated by TBI and contribute to late neurological dysfunction.[70] Persistent microglial activation can lead to oxidative stress that will, in turn, contribute to the development of progressive structural changes and long-term functional deficits.[69,116,117] Chronic structural changes after stroke and TBI are observed as axonal damage.[118,119] This late axonal damage is associated with the presence of microglial clusters.[120] Microglial activation can also contribute to neurodegeneration through the production of free radicals, such as nitric oxide, which impair mitochondrial function and lead to cell death.[121–123] A self-propagating cycle may occur as oxidative stress increases the production of free radicals from damaged cells. Inflammatory responses associated with increases of free radicals are also likely to be exacerbated with aging. Microglia have a low turnover after early development. This low turnover is compensated by their notable longevity.[124] Given that microglia are more likely to be in an alert or primed state during aging, their longevity makes them sensitive to oxidative stress and inflammatory exposure over time.[91]

In vitro studies have shown that, during inflammation, microglial stimulation by toll-like receptors (TLRs) may impair microglial ability to distinguish between viable and dead cells leading to excessive phagocytosis.[125,126] In addition, TLR-activated microglia release oxidants that increase neuronal phosphatidylserine exposure.[78,127,128] Phosphatidylserine, a neuronal "eat me" signal, can be notably upregulated and has been observed to result in axonal loss.[129] Increases in phosphatidylserine will also contribute to BBB disruption through multiple mechanisms, such as activation of matrix metalloproteinases (MMPs). MMPs disrupt proteins in the intercellular tight junctions that seal gaps within the BBB. In addition, it is well known that increases in cytokines such as IL-1β, IL-2, TNF-α, and IFN-γ contribute to the death of myelin-producing oligodendrocytes, resulting in white matter damage.[130–132] Axonal demyelination not only lessens the ability to transmit signals, but also increases axonal susceptibility to degeneration.[133] Hence, increases in cytokines have been associated with neurodegenerative diseases, such as PD and AD.[134,135]

Microglial activation is also triggered by β amyloid protein that results from the cleavage of amyloid precursor protein (APP). APP levels are increased in response to tissue damage due to its role in synaptic formation and repair.[136] Multiple neurological diseases, such as AD, feature amyloids. AD-like neuropathology is frequently observed after TBI.[137] In AD, microglial morphology changes are most evident in areas of high β amyloid concentration.[138] Microglial activation in the hippocampus of AD patients correlates with decrements in cognitive function and memory.[139] Impaired clearance of β amyloid in AD results in impaired neuronal signaling and microglial activation.[127] However, microglial clearance of β amyloid plaques is impaired in AD[140] although a direct causal linkage has yet to be substantiated. That the onset of AD in individuals who had sustained TBI was accelerated by about 10 years when compared to an AD population without prior TBI has been shown.[141]

The dual action of microglia and cytokines

As mentioned above, microglia are associated with both inflammatory and anti-inflammatory responses. These are respectively coupled with M1 and M2 stages. Microglia produce anti-inflammatory cytokines, such as IL-4 and IL-10, during M2 activation. However, the potentially protective effects of the M2 stage may be limited in TBI. Ym1, an M2 activation marker that prevents the degradation of extracellular matrix components, is upregulated for about a week and then is undetected at 3 and 12 months. This suggests that inflammatory markers are enduringly upregulated while their reparative counterparts appear to become chronically downregulated.[70]

Besides the production of anti-inflammatory cytokines, microglia can also have a restorative role by facilitating increases in neurotrophins, glutamate transporters, and antioxidants.[142–144] Although further research is necessary to determine how these microglial functions are affected with TBI, there is evidence indicating that microglia may offer protection after injury.[145] Different microglial roles may be dependent on the level of cellular damage, where

a protective and rescue function can switch to a cleanup and contain function. Microglia's motility and process outgrowth is regulated by neuronal activity.[146,147] Thus, it is not surprising that areas with significant tissue damage show less microglial activity as indicated in the TBI-PET study by Ramlackhansingh, described above. Microglial activation in areas remote to the site of injury may enhance or promote neuronal repair.[148,149] Accordingly, nonhuman primate studies indicate that microglia in remote areas continue to release brain-derived neurotrophic factor (BDNF) months after injury.[149] BDNF has well-established effects on neuronal survival and synaptic plasticity.[149–151]

Microglia's monitoring capabilities allow it to have an influence on experience-dependent plasticity through mechanisms such as synaptic stripping.[152] This mechanism may occur during experience-dependent learning given that synapse formation and elimination is an integral component of learning processes.[153] Although microglia-dependent synaptic pruning is most notable during brain development,[154,155] it is also observed in the adult brain. For example, live imaging of visual cortex has shown microglial stripping of inactive synapses.[156] Synaptic stripping may diminish energetic demands from weakened neurons that are metabolically compromised.

In addition, there is evidence that microglia may enhance neurogenesis. Although neurogenesis is most prevalent during development, it has also been observed in the adult brain[157,158] and after brain injury.[159–161] Microglia promotes insulin-like growth factor-1, which suppresses apoptosis and augments the proliferation and differentiation of stem cells[162] or may increase neurogenesis by facilitating oligodendrocyte-promoting cells to adopt a neuronal phenotype.[163]

This dual action observed in microglia also applies to some cytokines. This should be taken into consideration particularly when addressing cognitive function after TBI. For example, IL-1β levels and its receptor antagonist are significantly expressed within the hippocampus, a region that is critical to memory.[164–166] This, and other cytokines, have been found to modulate synaptic function[167,168] and long-term potentiation, a cellular correlate of learning and memory.[169–171] Accordingly, IL-1β plays a role in the consolidation of context-dependent memory when its levels are relatively low. In contrast, when IL-1β levels are abnormally increased, hippocampal function is impaired.[172,173] Under normal conditions, neurons and microglia are constantly communicating; however, under certain conditions, such as prolonged stress and injury, changes in IL and TNF-α levels can lead to neurophysiological alterations, such as increases of intracellular calcium that will increase cell vulnerability and neurodegeneration.[174,175]

It is evident that inflammatory responses contribute to the prolonged neurodegeneration that is frequently found after TBI. It is likely that the double-edged aspect of immune responses is dependent on tissue integrity and numerous ongoing pathophysiological processes. A better comprehension of mechanisms associated in microglial responses may provide therapeutic opportunities.

MITOCHONDRIA

Mitochondrial function is crucial to the energy demands of the CNS. Adenosine triphosphate (ATP) production from conversion of oxygen, glucose, and pyruvate to ATP occurs in mitochondria located throughout the cell body, axons, and dendrites.[176] Mitochondrial toxins, such as oxide, hydroxide, and peroxynitrate, are produced as a result of this metabolism. These substances are active in both neuronal signaling and in degeneration.[177,178] Mitochondria contain several protective antioxidants, such as coenzyme Q10 (ubiquinone), creatine, and nicotinamide.[179,180]

Fast, anterograde axonal transport along cytoskeletal tracks convey organelles and their proteins from their major sites of biosynthesis in the cell body to their sites of use and residence in the axons and terminal. Mitochondria participate in axonal transport via a bidirectional flow. This process works to position proteins along specific axon locations. Mitochondrial migration and positioning are responsive to focal energy demands within the cell, axon, or dendrite (Figure 1.2).[181]

Mitochondrial stress is increased during oxygen or glucose deprivation and with decreased calcium homeostasis. This energetic deprivation occurs after TBI, particularly during the acute period. Mitochondrial toxin production also increases with mitochondrial stress. Mitochondrial stress increases with alteration of fuel availability; ROS production; or increases in oxidative stress, lipid peroxidation, amyloid precursor protein, intracellular b-amyloid, cytokines, caspases, calpains, or cytochrome C.

Mitochondria are responsible for programmed cell death or apoptosis.[182] Mitochondrial alterations occur following excessive sequestration within the mitochondria of CA^{2+} or calpain-mediated alteration. This results in the opening of the mitochondrial membrane permeability pore that, in turn, induces the release of apoptosis protease activating factor 1, caspase-9, and cytochrome C.[183–186] This results in the activation of the caspase death cascade and constitutes an agonal event for the cell.[187] H_2O uptake and swelling occur followed by local energy failure and uncontrolled ionic homeostasis.

Mitochondrial function has been implicated in ischemic stroke, AD, PD, Huntington's disease, ALS, depression, bipolar disorder, and schizophrenia.[177,188–190]

MYELINATION

Myelin impacts the efficiency of axonal function and axonal health.[191] Remyelination occurs as a regenerative process in which new myelin sheaths are formed on demyelinated axons. Myelin repair consumes a great deal of the brain's daily energy consumption.

Remyelination has four stages: 1) oligodendrocyte progenitor cell (OPC) proliferation, 2) migration of OPCs toward demyelinated axons, 3) OPC differentiation, and 4) interaction of premature oligodendrocytes with denuded axons.[192] Remyelination has a different structural appearance

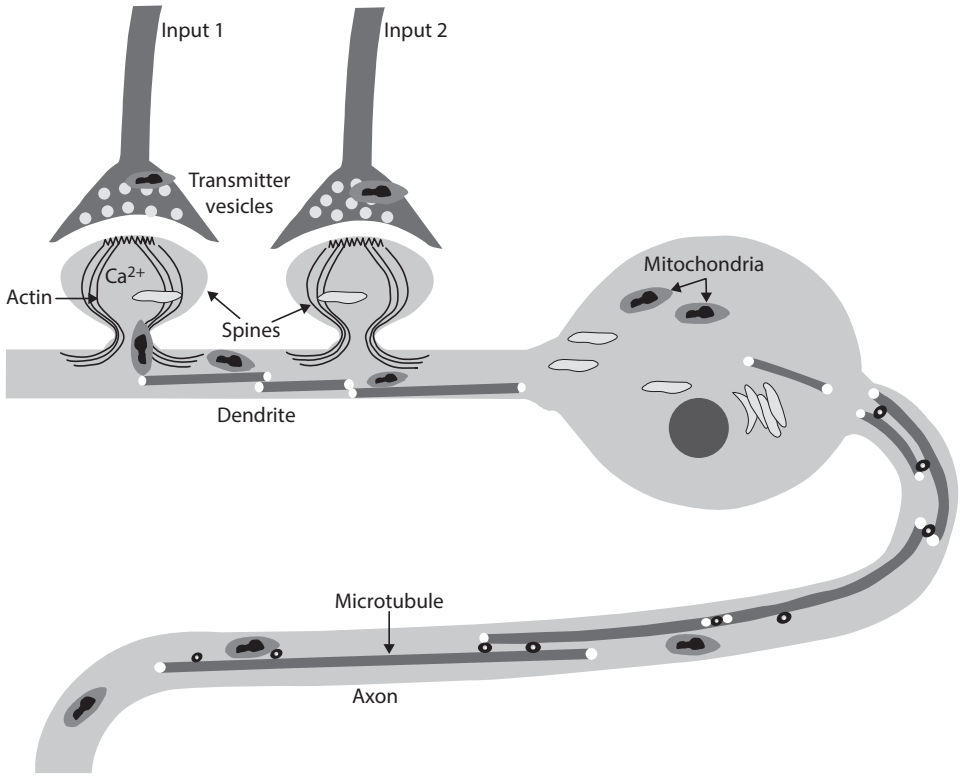

Figure 1.2 Involvement of mitochondrial motility in synaptic plasticity. Mitochondria migrate along microtubules in dendrites and axons. Mitochondria migrate to areas of greater energy demand as needed, such as dendritic spines and transmitter vesicles. (From Mattson, M.P., Gleichmann, M., and Cheng, A. Mitochondria in neuroplasticity and neurological disorders, *Neuron*, 60, 748–766, 2008. With permission from Cell Press.)

compared to developmental myelin.[193] Remyelination is thinner and results in wider nodes of Ranvier. However, conduction velocity is restored in remyelination along with axonal protection.[193]

Astrogliosis refers to glial scarring. Glial scarring creates a physical barrier that prevents OPCs and axons from entering demyelinated plaques, thus inhibiting remyelination.[194] This inhibition is mediated by astrocyte-derived chondroitin sulfate proteoglycans.[195] Ephrins are also released by astrocytes and bind to regenerating axons causing a collapse of the axon growth cones.[196] TNF-α, expressed by astrocytes, is implicated as a potentially causative factor in demyelination and oligodendrocyte pathology.[194,197,198]

Microglia and astrocytes play crucial roles in remyelination. Microglia remove myelin debris from demyelinated axons as an early trigger to remyelination. Phagocytosis of debris is closely accompanied by release of neurotrophins and cytokines, such as IGF-1, fibroblast growth factor-2 (FGF-2), TNF-α, IL-1β, ciliary neurotrophic factor (CNTF), leukemia inhibitory factor (LIF), platelet-derived growth factor-α (PDGF-α), BDNF, and neurotrophin-3 (NT-3).[191] A microglial phenotype has been identified associated with removal of myelin debris and apoptotic cells and with recruitment of OPCs to a lesion site via signaling by expression of cytokines and chemokines.[199] A complex signaling cascade, involving proinflammatory and anti-inflammatory cytokine production and neurotrophins, occurs between microglia and astrocytes to carry out the stages of remyelination described above.[198,200]

IGF-1 is produced by astrocytes and microglia and has been shown to promote remyelination.[201] Reduced expression of IGF-1 has been linked to profound delays in OPC differentiation into mature oligodendrocytes and proper remyelination.[202] IGF-1 has also been shown to prevent mature oligodendrocyte apoptosis in cuprizone exposure models of toxic demyelination.[202]

Demyelination is associated with the appearance of astrocytes and microglia and can play both beneficial and detrimental roles in MS.[194,197] Spontaneous remyelination occurs, but its efficiency is limited in MS.[203,204] Failure of OPCs to differentiate into myelinating oligodendrocytes contributes to pathogenesis of MS.[205]

NEUROENDOCRINE FUNCTION

Neuroendocrine dysfunction following TBI has now been well documented.[13,19,206–209] The presence of posterior pituitary dysfunction and its resultant disorders of salt and fluid balance have long been recognized by clinicians due to the ready availability of laboratory evidence routinely collected during the acute stages of recovery following TBI as well as the potentially life-threatening consequences of posterior pituitary dysfunction. Greater awareness has developed for

the evolution of anterior pituitary dysfunction following TBI as well. Prevalence of deficiency along the four primary hormone axes is reported as follows: somatotroph—6% to 25%, gonadotrope—8% to 12%, thyrotrope—4% to 6%, adrenotrope—4% to 6%.[19,206,211–217] However, it should be noted that the prevalence of deficiency along the four primary axes appears to vary with temporal proximity or distance from the actual injury. More detailed discussion of neuroendocrine function can be found in other chapters of this text.

Guidelines exist for screening for hypopituitarism following TBI.[218–220] The premise behind the timing of current guidelines is that most individuals will recover from endocrine dysfunction following TBI. In addition, there is uncertainty about the implications for endocrine supplementation in the acute recovery after TBI. It is probable that, as more information is collected regarding the impact of endocrine dysfunction and potential benefits of hormone replacement following TBI, that the clinical guidelines for screening and provocative testing will change accordingly.

Hypopituitarism may not manifest immediately after injury and may take months or years to do so.[221] There is some suggestion that the endocrine dysfunction identified at 6 months postinjury persists beyond 1 year in a majority of patients.[212] There are some anecdotal cases of partial spontaneous recovery of posttraumatic hypopituitarism although recovery appears to be somewhat rare.[222,223]

The brain and nervous system produce steroids, referred to as neurosteroids, *de novo* and join the gonads, adrenals, and placenta as steroidogenic.[224–227] Neurons and glia are involved in neurosteroid production, and production varies with location within the brain and distance from cell bodies.[228] Mediation of neurosteroids is accomplished by direct or indirect modulation of neurotransmitter receptors or through ion-gated neurotransmitter receptors. Neurosteroid stimulation of neurotransmitter receptors is manifested by behavioral change, e.g., stimulation of $GABA_A$ receptors, resulting in decreases in anxiety, sedation, and seizure activity.[229–239] Neurosteroids are considered to be broad-spectrum anticonvulsants and impact depression, learning, and memory; premenstrual syndrome; and alcohol withdrawal and, consequently, may merit consideration as an endocrine contribution to clinical manifestation of ABI.[240] Hormone steroids act as chemical messengers and are synthesized from cholesterol. The major classes of steroid hormones include progestogens, androgens, estrogens, and corticosteroids.

Hormone replacement therapy (HRT) is not yet routinely performed following TBI. There are several questions regarding HRT: 1) Does the patient benefit by returning hormone levels to within a normal range and, if so, how? 2) Is reacquisition of cortical function by residual neurological structures dependent upon or enhanced by HRT? 3) Does HRT impact the return of normal neuroendocrine function following TBI? 4) What are the potential complications of HRT, and does it worsen risk of the development of complications following TBI? 5) To what extent, if any, does neuroendocrine function impact the bioenergetics of brain function? 6) To what extent, if any, does HRT affect the pathogenesis or progression of other neurodegenerative diseases? These questions, coupled with unclear evidence regarding the *safety* of gonadal HRT, have limited both research and clinical practice. For instance, HRT has been implicated in increase in thrombogenesis and cerebrovascular and cardiovascular risk although it is unclear as to whether these risks can be mitigated by appropriate monitoring of blood chemistry during replacement. Further research has subsequently refuted some of this risk, yet the concerns about safety remain widespread.[241,242]

Crucial to determination of efficacy of such interventions is whether assessment of the effects of treatment is properly defined. Independent variables, such as rate and extent of recovery versus recovery of function alone, may be pertinent. Expectations pertaining to recovery of function may be tempered by the knowledge that the intent of HRT is for both immediate and long-term effects. HRT may play roles in neuroprotection, neuroactivation, growth promotion, and cellular therapy because endogenous hormones have such effects. HRT may also have an effect on disease prevention or mitigation.

Some hormones are synthesized on a local basis by neurons and glia within the CNS. It is not clear to what degree mechanisms responsible for endogenous localized production of hormones are affected following injury to the brain.

We shall review the impact that a few major hormones have on cellular function, regeneration, and repair.

Somatotrophic axis

Growth hormone (GH) dysfunction is the most prevalent endocrine dysfunction after TBI.[19,206,207,210,212,214,215,243,244] GH production is pulsatile in nature and tied to both slow stage sleep cycle production and to exercise. Serum levels of GH are unreliable as a measure of GH secretory production.[245,246] IGF-1 derives from GH metabolism as a major GH-dependent peptide and is used as a surrogate biomarker of GH production. However, clinical studies into the impact of IGF-1 both as a surrogate biomarker and a correlate of GH function have been mixed. IGF-1 levels following TBI should be monitored and provocative testing strongly considered for any IGF-1 levels below 200 μg/dl. Stimulation testing is necessary to most accurately determine whether GHD is present or not.[220] IGF-1 testing alone may be misleading because approximately 50% of adults with GHD have normal IGF-1 levels.[247]

In a study comparing IGF-1 serum levels to GH provocative testing via glucagon stimulation, a large number of patients with TBI whose IGF-1 levels appeared within normal ranges were actually GH deficient upon provocation testing.[248]

Exercise increases peripheral and intracerebral GH and IGF-1 in adult animals and results in similar increases in hippocampal neurogenesis.[249] Exercise has been shown to preferentially impact learning and memory, functional

recovery after brain injury and mental decline associated with senescence.[250–253] Underlying this improvement appears to be increases in BDNF within the hippocampus.[254] IGF-1 appears to mediate the impact of exercise on cognitive function.[255]

GH levels in the blood derive primarily from pituitary function, and IGF-1 derives primarily from the liver. It is well established that IGF-1 from the body reaches the brain parenchyma and CSF.[256] There is evidence to suggest that levels of both GH and IGF-1 are derived from amounts that cross the BBB as well as to amounts that may be produced in various parts of the brain.

GH and IGF-1 are implicated in neuroprotection, neuroactivation, growth promotion, cell therapy, regeneration, and functional plasticity.[256,257] The structural effects of GH and IGF-1 exerted include myelination, somatic growth, oligodendrocyte biogenesis, and dendritic arborization. Metabolic effects of GH and IGF-1 are found in production levels of neurotransmitters and neurotransmitter receptors, glucose metabolism, and mitochondrial function. Impacted neurotransmitters include serotonin, norepinephrine, dopamine, glutamate, and acetylcholine.[256] As a cell therapy, GH stimulates cellular protein synthesis, facilitates glucose metabolism, and promotes mitochondrial function.[258,259] Cellular enzymatic homeostasis supporting normal cellular function, including maintenance, repair, and normal metabolic function, is altered, in turn, by impaired protein synthesis.[260]

The trophic effects of GH within the CNS have been demonstrated for neurons and astrocytes.[261] GH affects both neuron and astrocyte proliferation in development, and conversely, decreased dendritic branching and smaller neuronal somas have been associated with lower GH levels.[262] GH appears to affect neuronal dendritic branching in the cerebral cortex[262] while IGF-1 affects arborization within the developing cerebellum[263,264] and the developing adult cerebral cortex.[265–267] Peripheral IGF-1 has been shown to increase both cellular proliferation within the dentate subgranular zone and the subsequent migration and differentiation of progenitor cells within the dentate gyrus.[268,269]

GH and IGF-1 appear to impact both angiogenesis and cerebral blood flow. Arteriolar density in the cerebral cortex in aged animals increases with GH treatment, and increased density was correlated with increased serum IGF-1 levels.[270] Additionally, brain vessel density in the hippocampus and cerebellum increases with IGF-1.[269] Elderly humans demonstrate an association of greater cerebral blood flow in the left premotor and left dorsolateral prefrontal cortices with higher IGF-1 levels.[271]

IGF-1 is effective in reducing damage following ischemic lesions in experimental animals; however, human studies have yet to be performed.[272] Administration of IGF-1 in animals reduces infarct volume and improves neurologic function after ischemia.[273,274] IGF-1 appears to enhance glucose uptake in neurons exposed to glucose deprivation,[275] and this may be one of the mechanisms exercised by estradiol as a neuroprotectant.[276] Glucose utilization was observed to increase from 11% to 14% in the anterior cingulate of the cortex, the CA1 region of the hippocampus, and the arcuate nucleus of the hypothalamus following IGF-1 administration in aged animals.[277]

Improvement in quality of life, body fat mass, lean body mass, bone metabolism, and low-density lipoprotein cholesterol were reported after 3 years of GH replacement in patients with adult onset GHD.[278] Quality of life improvements, increased satisfaction with physical activity, and decreases in health care consumption were noted in men and women with adult-onset GHD who received GH replacement.[279]

IGF-1 was found to positively correlate with cognitive functioning and overall degree of improvement following rehabilitation for individuals with ischemic stroke.[280] Outcomes were significantly better for those with IGF-1 levels above 161.8 μg/dl.

GH and IGF-1 have been the subjects of a number of research articles into various aspects of functioning following TBI. The most studied area has involved the association of GHD or low IGF-1 with fatigue. Most of these studies have had mixed results.[215,281–285] GH administration immediately following lesions to the motor cortex combined with rehabilitation resulted in significant improvement in motor function recovery despite the severity of the motor lesion.[286] Information processing efficiency, short-term memory, working memory, attention, set shifting, and visual processing improved after GH administration in TBI.[287,288] Neuropsychological performance was found to be preferentially improved in a group of patients with chronic TBI receiving GH replacement in combination with cognitive therapy up to 10 years postinjury in the cognitive parameters on the Wechsler Adult Intelligence Scale of understanding, digits, numbers, incomplete figures, similarities, vocabulary, verbal IQ, and total IQ in comparison to a control group receiving cognitive therapy only.[289]

In summary, GH and/or IGF-1 interact with oligodendrocytes, neurons, astrocytes, blood vessels, and erythrocytes within the CNS impacting along with neurogenesis, gliogenesis, glucose metabolism and cellular survival, protein synthesis, cerebral blood flow, neurotransmitter synthesis and reception, gap junction formation, myelin sheath formation, and arborization.[256,258,290,291] IGF-1 has been shown to reduce postischemic loss of oligodendrocytes and associated demyelination.[291] Given early indications of positive anatomic, physiologic, and functional impacts of GH replacement, attention paid to these substances in the postinjury phases following TBI or other brain injury may well provide for enhanced neuroprotection, metabolic and physiological functioning of residual structures, enhanced synaptic remodeling during learning and skill acquisition, better neuromodulatory availability and function, and perhaps more complete and rapid recovery of CNS capacity. Further, GH and IGF-1 may play important roles in prevention or mitigation of other neurodegenerative diseases associated with prior TBI.

Gonadotroph axis

Three concerns emerge in relation to gonadotropic hormones. The first has to do with potential disruption in the hypothalamic–pituitary–gonadal (HPG) axis arising from structural involvement of the hypothalamus or pituitary. The second has to do with secondary impact to the HPG associated with changes in other endocrine or immune system functions. An example of this might be found in increased production of aromatase, an enzyme that is critical in estrogen synthesis, and associated with increased adiposity. Hypogonadism is associated with male obesity. In contrast to primary hypogonadism, which stems from testicular failure, secondary hypogonadism involves the failure of hypothalamic–pituitary function. Adipose tissue will affect testosterone levels by aromatizing testosterone into estrogen at greater than normal amounts. The third concern arises with age-related declines in gonadotrope production. Although frank deficiencies may not be apparent following ABI, reductions in an individual's gonadal hormone production may go unheralded and take on greater significance with aging, in effect entering andropause or menopause earlier than the individual might have without ABI. In the instance of age-related dysregulation of the HPG axis, there is some suggestion that neurodegenerative senescence may be accelerated.[292]

TESTOSTERONE

Testosterone is a gonadotrope produced by the Leydig cells of the testes in men and the ovaries in women with lesser amounts produced by the adrenal gland cortex.[293,294] Testosterone is a neurosteroid and can be synthesized *de novo* in the CNS.[228]

Interestingly, neuronal steroids that are synthesized within the nervous system by neurons and glial cells appear to exert neurotrophic action with some showing an anticonvulsant effect.[295–297] Cholesterol is a fundamental steroidal precursor to testosterone, which, in turn, is a precursor to neurosteroidogenesis, specifically androstenediol and estradiol.

Testosterone crosses the BBB in the free form and influences neuronal cells.[298] Increases in neurite outgrowth in cultured neural cells have been observed.[299–301]

Androgens alter the morphology, survival, and axonal regeneration of motor neurons. Androgen receptors are found throughout the brain, and their distribution shows a sexual dimorphism.[302–304]

Testosterone is acted upon by the estrogen-synthesizing enzyme aromatase and converted to estradiol. Aromatase, itself, plays an important role in neuroprotection[305] and the neuroprotective benefits of androgens appear to be mediated by their conversion to estrogens.[306,307]

As neuroprotection, testosterone may exert protection against neurodegeneration by the prevention of tau protein hyperphosphorylation.[308] Tau proteins are predominantly axonal microtubule or binding proteins that stabilize the neuronal skeleton.[309] Increased plasma amyloid-β levels have been reported with androgen deprivation,[310] and reduced amyloid-β mediated apoptosis has been reported.[311] Reduced serum testosterone has been demonstrated in men with Alzheimer's disease.[312] Amyloid-β formation may be prevented by decreases in amyloid-β peptides after treatment with testosterone.[313] Testosterone effects a synergistic stimulation of protein synthesis with the cytokine IGF-1 and others.[314] Interestingly, testosterone levels are significantly lower in both men and women with ALS, a progressive disease that targets motor neurons.[315]

As a growth promoter, testosterone increases expression of nerve growth factor and mediates neurite growth and interneural communication via branching and arborization.[316,317] Testosterone increases the rate of axonal regeneration via selective alterations of the neuronal cytoskeleton in peripheral nerves.[318]

Testosterone has been shown to enhance spatial cognition in healthy men aged 60 to 75 years when testosterone levels were increased to a level commonly found in young men for 3 months.[319] Testosterone enanthate supplementation for 6 weeks improved spatial and verbal memory in healthy older men aged 50 to 80 years.[320] Another study showed improved working memory following testosterone enanthate.[319] Alleviation of depression has been observed with testosterone supplementation in individuals with low testosterone levels, including those suffering from treatment-resistant depression. An improvement in verbal and spatial memory in aging men has also been observed with testosterone supplementation.[321–323]

Androgen precursors have been shown to affect functional outcome in rats following experimental brain injury. In one rodent study, DHEA administered 1 week postinjury resulted in a significant improvement in physical and cognitive function.[324] Studies in humans after TBI have also suggested a correlation between functional status and testosterone levels.[283,325] In these studies, length of stay and functional status at admission and discharge were positively correlated with serum testosterone levels. There are a number of mechanisms by which this may occur, both physically and cognitively. Testosterone administration has been shown to improve cognitive function in males with AD, but not in women.[326] Testosterone replacement for hypogonadal males following TBI is currently under investigation in a small study in the United States (Figure 1.1).

ESTROGEN

Cholesterol is a fundamental steroidal precursor to the formation of estrogens. Estradiol, a naturally occurring estrogen, is synthesized most immediately from testosterone via the enzyme aromatase and, as a neurosteroid, can be produced *de novo* within the brain.[228] Aromatase enzyme production in glial cells is rapidly upregulated at the site of injury suggesting that aromatase, itself, may be active in neuroprotection or may exert neuroprotection via estrogen synthesis.[327]

Gender differences in outcomes following TBI have led to a number of studies investigating the impact of female steroid hormones on neuroprotection and neurogenesis

following TBI.[328] Initial efforts focused on estrogen as the potential source for these differences. Estrogen has a number of properties that make it a unique candidate for investigation into its potential for clinical intervention following TBI. The role of estrogen in neuroprotection from oxidative stress is considerable and includes serum deprivation, amyloid-β peptide-induced toxicity, glutamate-induced excitotoxity, hydrogen peroxide, oxygen–glucose deprivation, iron, hemoglobin, and mitochondria toxins.[329–352] Estrogen's neuroprotective effects have also been demonstrated in a number of models of acute cerebral ischemia and subarachnoid hemorrhage.[353–360] Although controversial, it appears that the neuroprotective mechanisms exhibited by estrogen do not directly affect neuronal structures but rather other cell types, such as astrocytes.[361]

Ischemia-induced learning disability and neuronal loss are prevented in both sexes by estradiol.[356,362,363] At the same time, when levels of estradiol are reduced, both the function and survivability of neurons are compromised.[364,365] Early onset and increased deposition of β-amyloid peptide in AD are associated with estrogen depletion in the brain.[366] Estrogen replacement can be effective as an early therapy for cognitive impairment in women with AD.[326]

There are some reports that raise concern estrogen may not be neuroprotective in all circumstances. Administration of estrogen prior to TBI was protective for males but worsened mortality in female rats in one study.[367] Transient forebrain ischemia has been shown to worsen hippocampal neuronal loss with estrogen.[368] Overall, there is some evidence that estrogen increases neuronal excitability while progesterone has anticonvulsant properties.[369] Estrogen promotes growth of glioma and neuroblastoma.[330] Interestingly, brain tumor after brain injury occurs in a higher than normal prevalence.[11] Additionally, the role of microglia in glioma removal seems important to consider as microglia function is abnormally altered after TBI.

As a cellular therapy, estrogens have a multitude of effects on mitochondrial function that are most notable when the cell is placed under stress. They are active in preservation of ATP production, prevention of production of ROS, moderating excessive cellular and mitochondrial CA^{2+} loading and preservation of mitochondrial membrane stability during stress.[370] Nonfeminizing estrogens have been found to be as effective as the potent feminizing hormone 17 β-estradiol (E2) in prevention of mitochondrial CA^{2+} influx,[371] and more selective neuroprotective synthetic estrogen-like compounds have been developed in response to the potential benefits of their use in treatment of neurodegenerative conditions.[372–376]

Estrogen receptors have been found to be selectively upregulated in certain areas of the brain following injury. Estrogen has important roles in modulating brain homeostasis, synaptic plasticity, cognition, and neuroprotection[377] through traditional and nontraditional cell-signaling mechanisms.[378–380] Some of the receptors code for specific genetic intracellular signals responsible for neurogenesis. In particular, some of these messengers, such as c-Fos and PELP1, appear to demonstrate properties responsible for activation of genetic mechanisms responsible for cellular repair. A potential area for clinical impact of estrogen may be in its apparent neuroregenerative properties. Some receptor-mediated responses may be responsible for causing stem cells to differentiate into neuroprogenitor cells and protect nerve cells from programmed cell death.[381–385]

PROGESTERONE

Progesterone, the body's main progestogen, has been implicated in a number of mechanisms that are important for neuroprotection following CNS insult. The effect of progesterone varies, like GH, depending upon the CNS compartment in which it is found. Its effects are mediated by estrogen priming within the hypothalamus and in some limbic structures. It is not mediated in the cerebral cortex, septum, caudate putamen, midbrain, or cerebellum.[386,387] In structures in which estrogen priming is involved, progesterone receptors are downregulated by progesterone treatment while they are unaffected in brain regions where estrogen priming is ineffective.[388,389]

The role of progesterone, as other hormones described above, is considered here primarily for its effects on neurophysiological function. The discussion of progesterone to follow refers to the natural hormone and its natural metabolites. Natural progestogens are metabolized in very different ways from synthetic progestogens, sometimes termed progestins. Technical issues pertaining to rationale for avoidance of specific progestins can be reviewed in Schumacher et al.[390]

Progesterone and its metabolites are effective in maintenance of neuronal viability and in regeneration of neurons. They also act on oligodendrocytes promoting myelination in the CNS and the peripheral nervous system.[390–393] Progesterone impacts remyelination[393] despite age-related declines in capacity for myelin regeneration.[394] The role of progesterone in remyelination is supported by an animal study showing better remyelination in middle-aged females compared to middle-aged males. No differences were found in younger-aged animals.[395]

Progesterone has been found to restore retrograde axonal transport.[396] Disruptions in axonal transport may contribute to the development of AD via stimulation of proteolytic processing of β-amyloid precursor protein.[397] Reduction of lipid peroxidation, also active in the development of AD, is achieved after TBI with progesterone treatment[398,399] along with increased activity of antioxidant superoxide dismutases.[400] Mitochondrial protection by increased expression of antiapoptotic proteins in the outer mitochondrial membrane has been demonstrated to be associated with both progesterone and estrogen.[401,402] In addition, female animals showed a complete reversal of mitochondrial respiration alterations with progesterone treatment at a low physiological range.[403]

Animal studies have also shown that progesterone reduces edema and secondary neuronal loss and improves recovery of function after TBI.[404,405] Neurons are

particularly susceptible to injury during cerebral ischemia benefit from progesterone.[406,407] Likewise, infarct size has been shown to be smaller in middle cerebral artery occlusion after pretreatment with progesterone.[408,409] When hormone administration is prolonged, behavioral recovery is more complete.[410] The timing of intervention has been shown to be effective ranging from preinjury treatment to up to 24 hours postinjury.[411]

Progesterone benefits have also been demonstrated in a human trial. Patients treated with intravenous infusion of natural progesterone for the first 3 postinjury days showed a reduction in mortality of 50% compared to patients treated with conventional state-of the-art treatment in the same facility.[412] Moderately injured patients treated with progesterone had better functional outcomes than nontreated patients. Another larger study, however, failed to find significant differences in outcomes for individuals who were administered progesterone after TBI.[413,414]

Thyrotroph axis

Thyroid hormones are the primary endocrine influence for regulation of metabolic rate. Thyroid is readily transported from the blood to the brain. It crosses into the brain via the choroid plexus and cerebrospinal fluid.[415] The active thyroid hormone, 3,5,3′, 5′-triiodothyronine (T3) is locally synthesized from thyroid (T4) by glial cells, tanycytes, and astrocytes via the action of type II deiodinase.[416] T3 is regulated by type III deiodinase to degrade both T4 and T3. Type III deiodinase is expressed by neurons.[416]

The role of thyroid in brain development may be instructive as to its potential role in the recovering brain. Thyroid deficiency during development impairs cytoarchitecture in the neocortex and cerebellum.[417] Changes in cortical patterns of lamination occur together with changes in dendritic morphology and axonal projections.[418,419] Cell migration, outgrowth of neuronal polarity, synaptogenesis, and myelin formation are slowed.[420] Glial cell proliferation and neuronal cell death are both increased.[420] Lastly, thyroid is also involved in microtubule assembly and polarization differences in axons and dendrites.[420]

Thyrotrophic dysfunction following TBI is less common than the somatotropic or gonadotrophic axes in terms of frank deficiency. Subclinical hypothyroidism, however, is common in adults without brain injury, and decreased resting energy expenditure has been found in those who have abnormally high TSH levels.[421] The risk for metabolic syndrome is raised in the presence of subclinical hypothyroidism.[422]

Thyroid has substantial impact upon mitochondrial function as it is involved in facilitating mitochondrial biogenesis and ATP generation.[423,424] The effect of thyroid on mitochondrial function is both nongenomic and genomic.[424]

Thyroid regulates gene-encoding proteins for a host of structures and substances. These include myelin, mitochondria, neurotrophins, cellular matrix proteins, cellular adhesion molecules, and proteins involved in intracellular signaling.[416,420]

CLINICAL IMPLICATIONS AND POTENTIAL THERAPEUTICS

It may well be time for development of active and complementary strategies for neuroprotection, neuroactivation, growth promotion, and cell therapies as routine approaches to patient management in chronic ABI. The hope for this chapter is to promote critical thinking about management of chronic disease arising from ABI. It is not possible to fully appreciate the interplay between primary injury and subsequent consequences that affect cellular metabolic dynamics, CNS connectivity, BBB integrity, inflammatory responses, and endocrine function. These, in turn, are influenced by aging, individual genetic variations, and medical comorbidities that may be present or emerge in later life.

Today, medical management of chronic brain injury is largely reactive. For example, pharmacological management of seizures and depression can have a notable influence on patient treatment. It seems worthwhile to consider whether chronic metabolic and endocrine challenges contribute to ongoing inflammation and BBB disruption as potential pathogenic contributors to other neurodegenerative diseases. Chronic disease management of ABI in the future should entail neuroprotective strategies, neurophysiologic optimization, cell therapies, growth promotion, and neuroactivation.

Clinical targets for rehabilitation medicine might include the following:

a. Alteration of mitochondrial respiration
b. Oxidative stress
c. Mitochondrial transport and aggregation
d. Microtubule/neurofilamentary integrity and repair
e. Membrane permeability maintenance
f. Cytokine production
g. ROS production and antioxidant protection
h. Protein and organelle biosynthesis
i. Oxygen or glucose deprivation
j. Cellular senescence
k. β-amyloid production
l. Microglial activation and function
m. Tauopathies
n. Lipid metabolism disorders
o. Superoxidase dismutase production
p. Oligodendrocyte function and biogenesis
q. Myelination
r. Myelin repair and preservation
s. Oligodendrogenesis and oligodendrocyte function
t. Neurosteroidogenesis
u. Hormone replacement therapies
v. Inflammation reduction strategies
w. BBB function, repair, and protection

Reconsideration of clinical management might include a greater role for endocrinology and immunology as well as the development of clinical biomarkers for such management. Today, rehabilitation medicine focuses on functional recovery in large measure. As our understanding of chronic disease mechanisms after ABI improves, it seems incumbent upon us to increasingly view the role of rehabilitation medicine as interventional and preventive medicine with far different treatment targets than simply function. An analogous approach in cardiology is the use of statins to retard or prevent more serious cardiovascular complications. Similarly, insulin replacement is undertaken to prevent downstream complications of prolonged high glucose levels.

Inflammation is known to be initiated by external stimuli, such as undesired pathogens or injury. Inflammation is also known to be self-perpetuating. So questions arise as to how much inflammation occurs after ABI, how long, when it is reinitiated and why. Might neurological function be improved if inflammation were to be reduced by interventions designed to interrupt an inflammatory cycle that is self-perpetuating or one that is triggered by inflammation elsewhere in the body as in microglial priming? Should medical management of a patient with prior ABI be different vis-à-vis a possible propensity toward CNS inflammation with unassociated illness? Might inflammatory processes, microglial function, BBB function and metabolic efficiency be improved by properly targeted HRTs? Can appropriate biomarkers for monitoring treatment be developed that are more indicative of biologic or physiologic processes? Finally, might conditions such as epilepsy, depression, and sleep disorders actually be symptoms of underlying and correctable endocrine or immune pathologies?

We must develop clinical diagnostic paradigms and strategies to enable clinicians to efficiently consider endocrine and immune contributions to disease management, mitigation, prevention, and cure. It is apparent that the clinical contribution of endocrinology and immunology must increasingly intersect with neurology, physiatry, internal medicine, and psychiatry. Once accomplished, we may come to find that we positively impact the incidence of neurodegenerative conditions associated with prior ABI.

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2

The neurobiology of traumatic brain injury

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INTRODUCTION

Although the neurobiology of traumatic brain injury (TBI) has been studied more in depth recently as technology has advanced in the field of neuroscience, some of the early seminal papers on the topic that proposed the pathophysiology and the biomechanics of TBI appeared in the early twentieth century.[1–5] The reader is encouraged to read these papers, as they provide a perspective of what was known in past decades and allow one to place the current review into perspective.

Probably one of the most important aspects of human TBI is its heterogeneity. Some of this is due to the complexity of the biomechanics associated with trauma to a very diverse and complicated structure. In addition, we now have a better understanding of the influence of age,[6–8] gender,[9] and chemicals/or recreational drugs that are on board during the insult.[10] However, these factors alone cannot explain all of the variance in TBI. The biomechanical nature of the insult and the response of different regions of the brain play an important role. Additionally, TBI is considered a continuum from mild to severe injury; however, the injury severity to different brain regions may vary in type and location of impact forces.

At the moment of injury, the brain is exposed to a number of different vectors of stresses and strains. Classically, these have been described in terms of acceleration–deceleration along with rotation. We now have a much better understanding through finite element modeling, which helps to describe what portions of the brain are at greater or lesser risk for sudden displacement at greater degrees.[11,12] As these stresses and strains are placed on the tissue, the white matter becomes stretched, and this contributes to one of the more important pathological findings in human TBI: that of axonal injury (sometimes referred to as diffuse axonal injury). Many investigators have studied the process of injury-induced disconnection and have concluded that nonmyelinated fibers are the most vulnerable[13] and that injury-induced disconnection is more prevalent than once thought.[14–24] This is not to suggest that neuronal cell death is unimportant, but it underscores the importance of addressing connectomics along with measuring the volume of regions/structures when assessing human TBI.[25–29]

WHAT HAPPENS TO THE CELLS IN THE BRAIN FOLLOWING TBI?

Following TBI, some cells are biomechanically and irreversibly damaged. Therefore, they can go through several different stages of cell death related to apoptosis, excitotoxicity-induced necrosis, and autophagy. Given the biomechanical distribution of TBI, this process of cell death can occur in many different regions affecting many different functions.[30–33] However, many cells survive the primary injury and go into a state of cellular vulnerability[34,35] and dysfunction. This vulnerability and dysfunction can be caused by many aspects of secondary complications associated with TBI (ischemia and intracranial hypertension just to name a few). However, if one steps back and reevaluates the basic neurochemical and metabolic disruptions of the brain following trauma, it is very clear that, although they are not the only factors compromising the injured brain, they certainly represent a good starting point.

At the moment of injury (which is severity dependent), cells in the brain are exposed to extensive discharges, causing the overstimulation of receptors and, in conjunction with the biomechanical stress and strain via mechanoporation,[36] breaks down the normal barrier between intra- and extracellular spaces. This would cause a number of changes

in the equilibrium, including a significant K+ efflux from cells due to mechanical membrane disruption, axonal stretch, and opening of voltage-dependent K+ channels.

In the normal brain, excess extracellular K+ is subject to reuptake by surrounding glial cells.[37–39] This compensatory mechanism can maintain physiologic extracellular K+ levels even after mild concussion or ongoing seizure activity[40,41] but is overcome by more severe brain trauma[42] or ischemia.[43–45] Initially, there is a slow rise in extracellular K+, followed by an abrupt increase as the physiologic ceiling for K+ balance is overcome. This triggers neuronal depolarization, release of excitatory amino acids (EAAs), and further massive K+ flux through EAA/ligand-gated ion channels. In the wake of this wave of excitation is a subsequent wave of hyperpolarization and relative suppression of neuronal activity,[46–50] a phenomenon termed "spreading depression."[51] One important difference between classic spreading depression and postconcussive K+ release is that TBI affects wide regions of the brain. Thus, loss of consciousness, amnesia, and cognitive impairment may be clinical correlations to post-TBI K+ release and a spreading depression-like state.

The TBI-induced depolarization of neurons leads to the release of the EAA neurotransmitter glutamate, which compounds the K+ flux by activating N-methyl D-aspartate (NMDA) and d-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptors.[52–57] In an attempt to restore the membrane potential, the Na+/K+ ATPase (which is energy dependent) works overtime, consuming glucose at a very high rate and producing lactate (see Figure 2.1). Concomitantly, the pathway for glucose metabolism is shifted following TBI with a larger percentage of the glucose that is consumed being shunted to the pentose phosphate pathway.[58–62] The problem here is not only the increased metabolic demand and a change in the metabolic fate of glucose, but that glucose itself is not stored within the brain, and the delivery of this fuel depends on the corresponding increase in cerebral blood flow (CBF).[63] These ionic shifts and acute alterations in cellular energy metabolism occur in a posttraumatic setting where CBF is diminished, although not to ischemic levels.[64] Rather, it is the mismatch between glucose delivery and glucose consumption that may predispose the brain to secondary injury. CBF may remain depressed for several days after TBI, possibly limiting the ability of the brain to respond adequately to subsequent perturbations in energy demand.

In addition to K+ efflux, NMDA receptor activation permits a rapid and sustained influx of Ca2+ (see Figure 2.1). Elevated intracellular Ca2+ can be sequestered in mitochondria, eventually leading to dysfunction of oxidative metabolism and further increasing the cell's dependence on glycolysis-generated ATP.[65–68] Calcium accumulation may also activate proteases that eventually lead to cell damage or death, and in axons, excess Ca2+ can lead to dysfunction and breakdown of neurofilament and microtubules.

Due to factors described above, ATP demand increases at the acute time period after TBI when ATP production is compromised, thereby triggering an energy crisis that may explain why the injured brain is so vulnerable to secondary insults.[69] As one would expect, given the high demand for glucose uptake and the low output of oxidative metabolism during this period of hyperglycolysis, there is also a commensurate increase in lactate production.[56] Interestingly, blocking the NMDA receptor or disrupting the glutamate pathway not only reduces the increase in extracellular K+ and the increase in uptake of glucose, but it also attenuates the production of lactate. After TBI, there is a period of time when all of these ionic and metabolic perturbations occur in regionally different areas. Also, depending on the area of the brain affected by the injury, the time course for these ionic and metabolic changes can be very different. In terms of the uptake for glucose, after a short period of time (in the rat, approximately 1 hour; in humans, it can be up to 4 hours, although the examples in Figure 2.2 are from a subset of subjects), the local cerebral metabolic rate for glucose (CMRgluc) decreases significantly below baseline, and the uptake of cellular Ca2+ continues to increase for

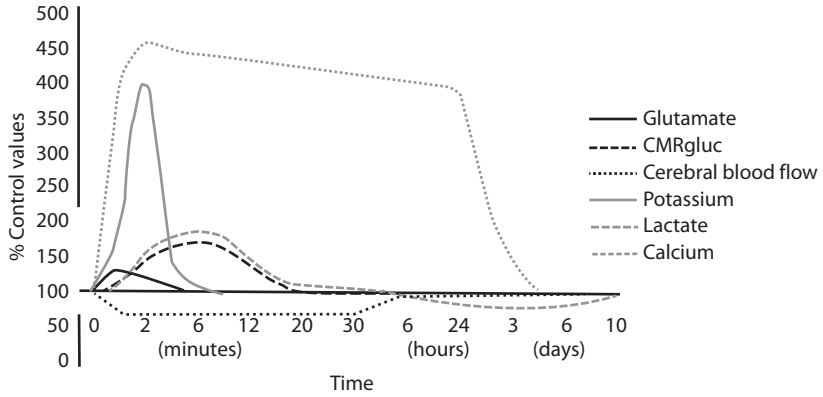

Figure 2.1 Measurements taken across time after the exposure to a mild traumatic brain injury in rodents using the lateral fluid percussion device. Cerebral microdialysis samples were measured for glutamate and potassium. Autoradiography was used for measurements of the cerebral metabolic rate for glucose (CMRgluc), cerebral blood flow, and calcium. Values are expressed as a percent of controls. Note the different time course for different aspects of the neurochemical and neurometabolic response to mild traumatic brain injury.

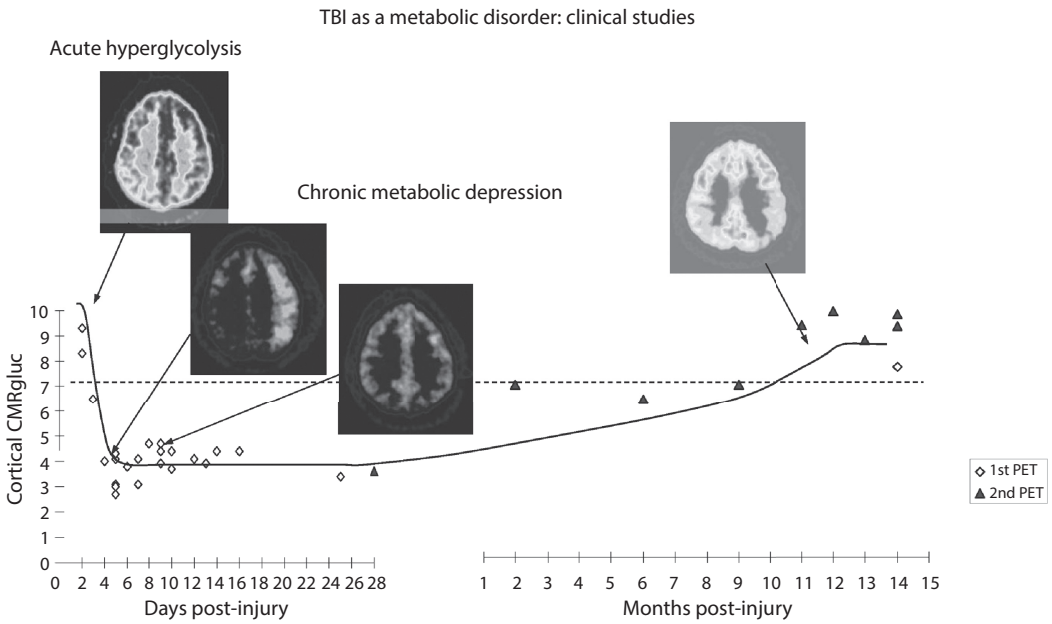

Figure 2.2 Human glucose time course. (From Bergsneider, M. et al., *Journal of Neurosurgery*, 86: 241–51, 1997; Bergsneider, M. et al., *Journal of Head Trauma Rehabilitation*, April;16(2): 135–48, 2001.)

several days after experimental TBI.[70] This increased Ca2+ is a likely mechanism for the reduction in oxidative metabolism after TBI, although changes in metabolic enzymes also contribute to impaired oxidative glucose metabolism.[71]

After the initial period of profound postinjury ionic disturbance and resultant increase in glucose metabolism, the local CMRgluc decreases (see Figure 2.2); this appears not to be injury severity dependent[72–74]. In the rat, this period of diminished glucose metabolism is seen in the cerebral cortex ipsilateral to injury as early as 6 hours after fluid percussion and does not normalize until between 5 and 10 days later (see Figure 2.1). In humans, it can begin during the first week and last for months (see Figure 2.2). Ipsilateral hypometabolism may also be seen in regions of the hippocampus at 6 hours postinjury in rats, generally normalizing by 24 hours. The precise mechanism of this phenomenon is, as yet, unknown, but it likely involves intracellular calcium accumulation and impaired mitochondrial oxidative metabolism. There is now some evidence that this period of diminished cerebral metabolism is protective,[75,76] and its length of time is shorter in younger animals.[77] Human patients with severe TBI show diminished CMRgluc in the postacute period.[78] It is interesting to propose that glucose metabolism may be an initial marker of the degree and extent of TBI (see Figure 2.3).

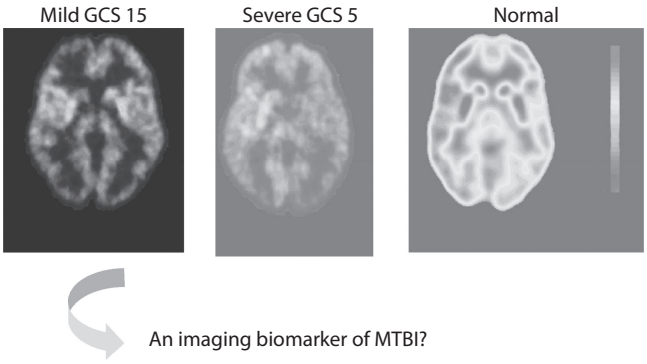

Figure 2.3 PET scans. (From Bergsneider, M. et al., *Journal of Neurosurgery*, 86: 241–51, 1997.)

OUTCOME MEASUREMENTS IN EXPERIMENTAL ANIMAL MODELS

A review of all the sensorimotor outcome measurements in animal models is beyond the scope of this chapter, but most of the literature cited herein includes results on learning and memory as well as motor functions after TBI. All of these measurements have different recovery time courses due to the severity of injury. Although there are deviations between studies regarding the actual tasks or techniques used, the majority report duration of deficits that correspond to the amount of tissue loss due to TBI. As reviewed recently, few studies have followed animals for a long period of time, allowing for chronic measurements of histopathology and recovery.[79,80] However, some of these deficits may be due to long-term dysfunctional issues rather than cell death per se. For example, it now appears that mild TBI in rats makes them more susceptible to fear conditioning,[81] creates long-term hormonal dysfunction,[82,83] and perhaps increases their vulnerability to toxins that can cause Parkinson's disease.[84]

LONG-TERM ISSUES WITH TBI

Addressing the neuropathology of human TBI has a long and distinguished history.[85–88] In addition, many studies

have addressed the long-term chronic neurologic problems (e.g., seizure disorders, Alzheimer's disease, dementia, Parkinson's disease, multiple sclerosis, amyotrophic lateral sclerosis) associated with human TBI.[89,90] More recently, there has been increased focus of brain pathology in cases in which mild TBI (otherwise known as concussion) has been endured.[18,23,24,91–99] Since 700 B.C., man has engaged in what would be considered organized sports and participation runs the risk of acquiring cerebral concussion. Furthermore, the clinical symptoms associated with concussions have been reported since the time of Hippocrates (for a historical review see McCrory and Berkovic[88]).

There has been considerable research on understanding the cumulative effects of concussion in terms of the long-term development of neurodegenerative processes that can contribute to a loss in quality of life as an athlete (and/or patient) continues to age. Prior to the development of sensitive brain imaging (before 1970), investigators were confined to postmortem studies that would allow the dissection and histological assessment of the central nervous system (CNS). To understand the neuropathological consequences of repeated concussion in human athletes, many investigators have focused on boxing.[100–103]

Studies in both amateur and professional boxers go back a number of years and primarily were driven by devastating consequences that resulted in a fighter's death. There were several case reports looking at the electrophysiological consequences of boxers who have received multiple concussions. However, the first series of conventional multisubject clinical investigations occurred in 1968 and 1969 with studies by Payne and Roberts.[104,105] One of the main points emphasized by Roberts (1969) was that examining the brains alone was not sufficient. Investigators needed information regarding the lives of these fighters both in terms of medical issues as well as psychological challenges. Then, in 1973, a comprehensive description of 15 retired boxers appeared in which a characteristic pattern of cerebral change was identified that was thought to be the result of boxing, but also perhaps was responsible for some of the features of dementia pugilistica[106] (punch drunk syndrome).[107]

It was well accepted that devastating blows to the head would result in brain pathology that would reflect itself in abnormalities of the septum pellucidum, brain scarring, degeneration of the substantia nigra, and formation of Alzheimer's neurofibrillary tangles. Beginning in the middle to late twentieth century, a change occurred in this area of neuropathology, and the concern that repetitive concussive blows, not previously recognized as a potential for concern, became an interest for neuroscientists who studied the physiology of concussion. Here, seminal papers appeared[1,108,109] that indicated even a mild biomechanical blow to the brain produced a substantial change in neurophysiology with some characteristics likened to spreading depression. Subsequent work with animals confirmed these changes in neurophysiology and began to describe the mechanisms by which brain cells that survived the biomechanical blow of concussion become extremely vulnerable to a second insult for a period of time.[34,55,110,111] This led investigators to explore novel ways to manage TBI in general and also fostered the effort to determine if there was a cost to the brains of athletes who experienced repeated concussions close in time. It has been recently proposed that one of these "costs" appears to be the development of chronic traumatic encephalopathy (CTE).

However, in a recent review,[112] the existence of CTE as a real disease has come into question. There currently are no controlled epidemiological data indicating an increased risk for any type of unique neuropathology in athletes. Nor is there an established clinical or pathological criterion for diagnosing CTE. This review lists a number of conditions associated with high levels of cerebral tau aggregation. Therefore, phosphorylated tau may not be the definitive and specific marker for CTE.

In early neuropathological studies of patients with mild TBI, investigators described the unusual finding of numerous neurofibrillary tangles in the cortex (particularly in the temporal lobe), but there was very little evidence of plaque formation, which is not typical of Alzheimer's disease.[107] This "extensive neurofibrillary change in the absence of plaque formation is a puzzling phenomenon."[113] Over the years, this has been described as an accumulation of hyperphosphorylated tau and has been termed CTE.[114–126] In the next section of this chapter, we address the question of whether there is experimental evidence for CTE in animal models of mild TBI as defined by the neuropathological finding of phosphorylated tau.

EXPERIMENTAL ANIMAL MODELS OF CTE AS DEFINED BY PHOSPHORYLATED TAU

Early experimental studies began to address the relationship between TBI and Alzheimer's disease by focusing on changes in the protein tau. Using a modified lateral fluid percussion model in the rat, animals were exposed to a single mild impact with others experiencing seven mild or moderate impacts every 24 hours.[127] Upon histological examination 1 week after injury, the neuronal perikarya within the ipsilateral cortex after repeated mild impact were clearly immunostained with tau-1 antibody. Enhanced tau-1 immunostaining in the deep cortical layers within the ipsilateral side was extended from the perikarya to the proximal area of the axons. Although not directly confirmatory, this may indicate that repeated mild brain impact could induce the accumulation of phosphorylated tau.

In another rodent study, brains were examined at 2, 4, and 6 months after lateral fluid percussion injury.[128] Phosphorylated tau measured using AT8 immunostaining was "weakly" noted in the superficial cortical neurons in the cytoplasmic perimeter and apical dendrites between 2 and 4 months post TBI. This immunostaining was more evident bilaterally in spinal tracts of the trigeminal nerve and was again weakly noted within the brain stem at 6 months. However, these investigators reported a 42% decrease of cortical neurons (as well as significant cell loss within the

dorsal hippocampus) at 6 months and a 64.5% mortality rate. Therefore, although tauopathy was demonstrated in animals after a single TBI, the level of severity was significantly higher than that typically seen in concussion.

Tran and colleagues investigated the relationship between amyloid-β (Aβ) and tau pathologies in the setting of TBI in a mouse model of Alzheimer's disease (3xTg-AD).[128] These animals normally develop intracellular Aβ accumulation starting at 2 months of life, intracellular tau immunoreactivity at 6 months, extracellular Aβ deposition at 15–26 months, and tau-containing neurofibrillary tangles at 26 months. Using the cortical controlled impact model, TBI independently resulted in intra-axonal Aβ and tau accumulation and increased tau phosphorylation in these mice.[129]

Goldstein and colleagues used a blast neurotrauma mouse model[114] to investigate blast forces on the skull of the mouse in acceleration–deceleration oscillation of sufficient intensity to induce persistent brain injury. Two weeks after being exposed to a single blast delivered through a compressed gas-driven shock tube, injured mice exhibited enhanced somatodendritic phosphorylated tau CP-13 immunoreactivity in neurons within the superficial layers of the cerebral cortex. In addition, hippocampal CA1 neurons were intensely tau 46-immunoreactive. In order to confirm the presence of phosphorylated tau proteinopathy, immunoblot analysis of tissue homogenates was performed. These samples demonstrated a significant blast-related elevation of phosphorylated tau protein epitopes pT^{181} and pS^{202} as detected by the monoclonal antibody AT270. These findings of CTE were compared and contrasted with other histopathological findings as well as to impairments in hippocampal neurophysiology. Along with studies of long-term behavioral deficits that were specifically related to head movement, these investigators appeared to be the first to demonstrate a CTE-like neuropathology in a mouse model of blast TBI, albeit only at a subacute phase with no longitudinal component to determine progressive neurodegeneration.

In a more conventional model of experimental rodent TBI, Hawkins and colleagues explored the accumulation of endogenous tau oligomers following parasagittal fluid percussion injury.[130] Rats were studied at 4 and 24 hours after injury using an anti-tau oligomer antibody. They were able to localize tau oligomers (T22) and pan tau antibody Tau-1 within the hippocampus and cerebral cortex at 24 hours after injury. When they extended their studies to 2 weeks after injury, oligomeric tau (T22) and phosphorylated tau (AT8) were again present in both the hippocampus and cerebral cortex.

These results suggested that tau oligomers, not neurofibrillary tangles, are responsible for the initiation and spread of tau pathology in the neuron, reminiscent of sporadic tau pathologies.[131,132] Therefore, it is possible that the elevated levels of extracellular tau following TBI[133] accelerate the formation of oligomeric seeds, leading to the spread of tau pathology in TBI. Such a unifying hypothesis has also been proposed with the thought that cellular stress may be the instigator for prions in neurodegenerative diseases.[134]

In most clinical neuropathological studies, there is an inference that the resulting CTE is related to the exposure of individuals to repeated concussions. In a recent experimental study using mice, this hypothesis was addressed.[91] Using a weight drop method without a craniotomy, mice were exposed to various combinations of repeated insults that varied from 5 days to 5 months with combinations of concussive insults (daily, weekly, biweekly, or monthly). Mice subjected to repeat mild TBI daily or weekly, but not biweekly or monthly, had persistent cognitive deficits as long as 1 year after their last injury. Although these deficits were associated with astrocytosis, they were not related to tau phosphorylation or amyloid β as measured by ELISA. Interestingly, these deficits were also unrelated to the formation of plaques or tangles (by immunohistochemistry), changes in brain volume, or changes in white matter integrity as measured using magnetic resonance imaging. From these experiments, it would appear that when repeat mild TBI occurs over a short period of time, subjects may be more susceptible to prolonged cognitive decline, and this may not be related to tau accumulation. Such a mild TBI-induced vulnerability has been reported in a rat model of closed head injury;[76] however, from an experimental perspective, the mechanism(s) related to the phosphorylation of tau (CTE) may not be restricted to the exposure of repeated mild blows to the head.

The hypotheses that repeat mild TBI may result in an increase in phospho-tau were also addressed in a mouse model by Kane and colleagues.[135] In this study, investigators developed a new model of experimental closed head mild TBI and reported a series of neurological, behavioral, and histological findings in mice that were exposed to single or multiple insults. When mice were injured once per day for 5 days and studied 30 days after the last insult, there was nearly a 160% increase of phospho-tau (compared to controls) within tissue samples containing the hippocampus and cerebral cortex. However, mice exposed to this injury regimen were not statistically different from controls in terms of locomotor activity at 30 days postinjury. Unfortunately, the investigators did not report findings related to learning and memory that may have revealed a related effect to the phospho-tau increases within the samples containing the hippocampus.

Using a repeat mild TBI model in mice, another study found that six concussive daily impacts for 7 days can result in many neurological, cognitive, emotional, and sleep disturbances with alterations in risk-taking behavior lasting for as long as 6 months. However, in this comprehensive neurobehavioral study, phospho-tau was not measured postmortem, so a direct comparison between these deficits resulting from repeat mild TBI could not be related to the classic marker of CTE.[136]

SUMMARY AND CONCLUSIONS

The pathophysiology of TBI is a complex process that begins immediately after biomechanical insult and continues throughout an extended time frame. This chapter described

several biochemical, metabolic, and neurochemical processes that may occur after injury. Many of these processes are injury dependent whereas severity of injury may determine the extent and duration of these alterations. This array of processes opens up the opportunity for treatments in the acute and chronic stages. For example, the use of a metabolically driven therapy is gathering momentum. Supplemental fuels including glucose,[137,138] lactate,[139–141] pyruvate,[142–144] and ketone bodies[145–147] could benefit post-TBI CMRgluc, reverse metabolic dysfunction, improve neuronal survival, and, in some cases, neurobehavioral. Although the administration of supplemental fuels has been shown to be efficacious in acute and subacute time points, it remains to be seen if they are effective in more chronic settings. The advent of new and more injury-specific biomarkers, including biofluid and neuroimaging modalities, will aid in the diagnosis and treatment of TBI across all levels of the continuum of injury.

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3

Repeat traumatic brain injury models

MAYUMI PRINS

INTRODUCTION

Traumatic brain injury (TBI) remains one of the most frequently occurring public health issues and is the number one cause of death and disability among children 19 years old and under. According to the 2003 report to Congress, mild TBI (mTBI) makes up approximately 75% of the annual 1.7 million TBI cases. Contributing significantly to the mTBI population are sports-related head injuries among teenagers and young adult athletes. Approximately 1.6–3.8 million sports-related concussive events occur predominantly among teenagers and young adults, a population among which the concussion rates are increasing. Emergency department visits for concussions among 8- to 13-year-olds has remained around 5,800 per year, and the rates among 14- to 19-year-olds has increased from 7,276 concussions in 1997 to 23,239 concussions in 2007.[1–3] Although the rate of concussions within the adolescent population continues to rise, several small-scale studies report the incidence of repeat concussions (RTBI) to constitute between 5.6% and 4.9% of the annual sports concussion cases.[4–8] Although epidemiological data is ongoing regarding the exact incidence of RTBI, there has been a rapid emergence of experimental RTBI models to address concerns observed clinically, including axonal injury, inflammatory responses, cognitive impairments, and long-term risk for neurodegenerative diseases.

The models

The goal of these injury device modifications is to model concussive or mTBI. Clinically, these types of injuries are closed head, mild level of severity, with low mortality rates that exhibit behavioral symptoms in the absence of gross neuropathology. Experimental models of concussion and mTBI should reflect these characteristics. It is important that new models of RTBI demonstrate the magnitude and time course of outcome changes with a single injury before repeating the injury. This ensures that a truly "mild" injury is additive when repeated. Establishing the number of impacts and intervals is also a critical aspect of RTBI models, and the rationale for the parameters used are often lacking and vary widely between studies.

These modeling parameters have been applied to previously well-established injury models (controlled cortical impact, CCI; weight drop, WD; fluid percussion, FP) to produce mild RTBI experimental models. The CCI injury was originally designed to produce a penetrating injury of known depth and velocity to generate an evolving contusion.[9] More recently, the CCI has been modified to achieve milder injuries. Modifications to the CCI injury include variations in the impactor tip size and material, stereotaxically restrained or free-moving head, exposed skull or closed head, and the distance and velocity of head displacement. The majority of CCIs remain lateral injuries, although

the injury can be delivered to any region. The WD injury was characterized to produce a central midline diffuse injury on the helmeted or exposed skull of rats on a foam pad.[10] More recent modifications to produce milder injuries include variations in the material supporting the animal (foam, foil, Kimwipe™), weight mass and distance of drop, and the presence or absence of a helmeted disc on the skull. The FP injury is another well-established model of diffuse brain injury that can be delivered laterally or centrally.[11] This injury requires a craniotomy and installation of a fluid-filled injury cap, which is attached to the pendulum device. Release of the pendulum generates a fluid pulse that travels down a tube into the injury cap and into the epidural space. Reducing the angle from which the pendulum is released can produce a mild injury, but production of repeat injuries at the same site can be problematic. Thickening of the dura and increased connective tissue to the edges of the exposed craniotomy after an injury can decrease the ability of subsequent fluid pulses to be delivered to the epidural space. This is a problem that is not often addressed in those utilizing FP injuries in RTBI models.

Experimental design

Experimental design is a critical part of any research, but there are specific design challenges in regards to RTBI models in the adult and developing brain. The selection of appropriately aged animals is important and directly dependent on the outcome measures of interest. Although making interspecies age comparisons is difficult, there are several reviews that address species age windows that represent infants, children, teenagers, and adults (Figure 3.1).

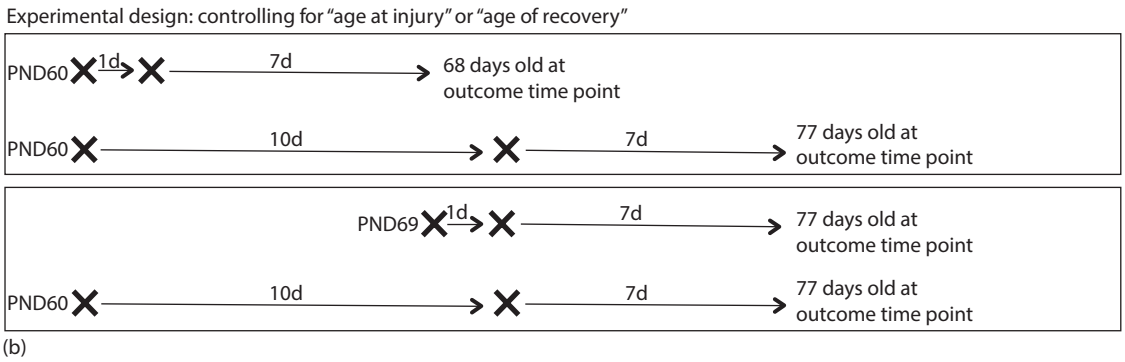
Knowledge of developmental profiles of the specific outcome measures in a given species is important for interpretation of TBI-induced effects. Outcome measures of interest can be particularly limiting when working with developing age groups. Although assessment of behavioral function after injury can be achieved in adult animals by comparing pre- and postinjury performances, this may not be possible with the younger animals if pretraining occurs before they are developmentally capable of performing the task. Determination of the appropriate interspecies age groups can also be challenging. There are several recent reviews on this topic that have assisted researchers in making more accurate age selections (Figure 3.1a). It is estimated that after adulthood is achieved, every 1 month for a rat is equivalent to 2.5 human years.[12]

RTBI studies require establishing a certain number of impacts and a time interval between them. A rationale should be provided for the selected number of injuries and the interval between injuries. Although this seems obvious, this is often lacking information and could be quite useful for other researchers. Upon establishing the injury groups, there can be a difference in the ages at which the injuries are

Interspecies comparisons for age selection

Human age	Rat age (postnatal days)	References
Newborn	PND 12–13	Romjin 199
Toddler 2–3 years	PND 20–21	Semple 2013; Sengupta 2013
Childhood 4–11 years	PND 25–35	Sowell 1999
Adolescent 12–18 years	PND 35–45	Andreolle 2012; Spear 2000, 2004; Giedd 1999
Young adult 20 years+	60 days	Andreolle 2012; Semple 2013
Adult 30 years+	12 months	Andreolle 2012

(a)



(b)

Figure 3.1 Experimental design considerations. **(a)** Interspecies age comparisons in selection of appropriate age of animal models. **(b)** Controlling for either age at injury or age at recovery of outcomes.

delivered and the ages at which outcomes are tested, if there are variations in the interval between injuries (Figure 3.1b). This may not significantly affect results when the interval is 1–2 days. But intervals of 1 week or greater can produce large differences in "age at the time of assessment," and this emphasizes the need for age-matched controls. Alternative designs include matching the age of outcome assessment and altering the age of injury (Figure 3.1b). The inability to control for both age and time after injury is a design limitation that often complicates developmental TBI and RTBI studies. These modeling issues should be kept in mind throughout the review below of RTBI models in the developing animal models and adult animal models.

REPEAT MILD TBI IN DEVELOPING ANIMAL MODELS

The incidence of TBI across all age groups has shown peaks in early development and adolescence.[13] Despite this evidence, the field of TBI as a whole has focused on adult models, and a similar pattern has emerged again in modeling for RTBI. There are far fewer animal models addressing repeat head injuries in the child and adolescent stages of brain development. RTBI in the younger child is addressed in a later section of this chapter.

Addressing RTBI in the adolescent brain is important for several reasons. First, as mentioned, adolescents are the peak TBI population with the peak incidence of all TBIs, including concussions. Among 14- to 19-year-olds, concussion rates have increased from 7,276 concussions in 1997 to 23,239 concussions in 2007.[1,2] More importantly, many adult athletes who are often studied for concussion effects often have a history of TBI starting during adolescence! Second, the adolescent population is at the greatest risk, as they are the least likely to comply with return-to-play guidelines. Their normal adolescent behaviors put them at greater risk for multiple concussions with shorter time intervals.[14] Third, the adolescent brain is in a critical stage of development. RTBI can alter the normal physiological, cognitive, and social development of the individual, leading to a lifetime of living with chronic difficulties that can impact their academics, ability to hold jobs, live independently, and be productive individuals. The economic burden and social stress that families experience largely goes unappreciated.

Adolescent RTBI

HISTOLOGY AND BEHAVIOR

In 2010, Prins et al.[15] were the first to use the 5 mm CCI impactor on a free-moving closed head to produce a concussive injury in an adolescent rat. This mTBI model was used to assess the effects of RTBI on various outcome measures, including histology, cognitive performance, pituitary function, metabolism, gender, and amyloid accumulation (Table 3.1). A single injury produced brief transient apnea, delayed toe-pinch response and righting response, acute cognitive deficits, and mild gliosis.[15] Increases in axonal injury, as indicated by amyloid precursor protein (APP) immunohistochemistry, were observed to a greater extent in RTBI (two injuries/24-hour interval) than single injury. Novel object recognition task deficits were not observed in single or RTBI groups when the interval between familiar and new objects was 1 hour. Increasing the duration between familiar and novel objects revealed increasing magnitude of deficits with number of injuries. Recovery of novel object recognition to sham level performances was observed at 3 days postinjury in those with single impact, but the RTBI group remained impaired.

BRAIN IMPACT INTERVAL INFLUENCES METABOLISM AND AMYLOID DEPOSITION

This CCI adolescent RTBI model was utilized to address the issues regarding brain impact intervals. Changes in cerebral glucose metabolism (CMRg) have been established as a hallmark response after experimental and clinical TBI. The magnitude and duration of TBI-induced CMRg depression increases with injury severity[16] and age.[17–19] Brain cells exposed to a concussion typically survive, but they exhibit neurochemical and neurometabolic dysfunctions, which not only contribute to neurobehavioral deficits, but also create a state of vulnerability.[20] This vulnerability can last for days to weeks, depending on the type and severity of concussion, and cells that normally would tolerate a concussive event are now compromised when exposed to a second injury.[21,22] Although the specific mechanisms behind this TBI-induced CMRg depression are unknown, recent findings have demonstrated that metabolic alterations[22,23] mark the window of cerebral vulnerability. The adolescent RTBI model was used to demonstrate that CMRg depression recovered by 3 days after a single mTBI in adolescent rat. When a second mTBI was introduced *during* the glucose metabolic depression of the first injury, it resulted in greater metabolic dysfunction and behavioral impairments. However, if the second TBI was introduced *after* the glucose metabolic depression of the first injury recovered, the metabolism and behavior effects were not exacerbated.[21] This was the first study to demonstrate that the brain impact interval directly affects metabolic outcome.

The brain impact interval has also been shown to influence amyloid accumulation in adulthood after RTBI during adolescence in the same CCI injury model.[24] Adolescent male and female APP/PS1 transgenic rats were given RTBI (four impacts/24-hour or 72-hour interval), and amyloid plaque load was determined at 12 months of age. Significantly greater size and number of hippocampal amyloid (Aß) plaque deposition were observed in RTBI at the 24-hour interval than those with RTBI at the 72-hour interval. Similar results were seen in extrahippocampal regions, and the increased Aß deposition was seen bilaterally in both males and females. This study was the first to demonstrate that RTBI during adolescence can accelerate deposition of Alzheimer's disease pathology and that these effects are dependent on brain impact interval.

Table 3.1 Animal models of repeat TBI in the developing brain

Type	Age/species	Injury specifics	Injury parameters	Anesthesia	Outcome measures	Single injury	References
CCI	Rat (PND35)	5-mm tip, 8-mm depth 36 psi, closed skin, no restraint	One or two impacts/1-, 3-, and 5-day intervals	Isoflurane	Histology, cognitive, metabolism, pituitary function, gender, amyloid accumulation	Yes	Prins et al.[15,21]; Greco et al. 2013[25], 2015[26]; Serpa et al.[27]; Grant et al.[28]
WD	Mouse (PND35-42)	Midline injury; 40 g from 1 m	One impact/2-day interval for 7 days; three impacts/2-day interval for 7 days	Isoflurane	Axonal injury, cell loss, neuroinflammation	Yes	Xu et al.[29]
WD (foil)	Mouse female (PND35)	Midline injury; 95 g from 1 m	Five impacts/24-h interval	Isoflurane	Bone mass	No	Yu et al.[30]
CCI	Rat (PND18)	9.5-mm rubber tip, 1-mm depth; 4 m/s velocity, restrained, skull exposed	One, two, or three impacts/24-h interval	Isoflurane	Histology and behavior	Yes	Fidan et al.[31]
WD (Kimwipe™)	Rat (PND20)	Midline injury; 92 g from 865 mm	Five impacts/24-h interval	Isoflurane	MRI	No	Goddeyne et al.[32]

PITUITARY DYSFUNCTION

Adolescence is a developmental period characterized by hormonal changes that are necessary for time-sensitive development of permanent brain structures, cognition, and behavioral function. More recently, the adolescent CCI RTBI model has been used to examine hypopituitarism following injury and determine the effects on growth and behavior. Adolescent male rats were given sham, single, or four RTBI/24-hour interval, and the time course of growth hormones (GH) and insulin-like growth hormone (IGF-1) changes were determined. RTBI resulted in decreased circulating GH and IGF-1 levels (1 week and 1 month postinjury), decreased body weight and sexual maturation and increased permeability of the pituitary vasculature.[25] RTBI also produced deficits in testosterone production, reproductive organ growth, erectile dysfunction, and impaired reproductive behaviors at 1–2 months postinjury.[26] These results demonstrate the risks of undiagnosed hypopituitarism after repeat concussions in the adolescent population, which can affect normal brain development and neurobehavioral function in adulthood.

The WD model has also been adapted to produce RTBI in adolescent female mice to address the consequences of hormonal changes.[30] PND38 rats were positioned on a taut foil during the impact of a 95-g weight dropped from 1 m, allowing the animal to freely move upon impact. The effect of a single injury was not characterized in this study, but five impacts at 24-hour intervals produced decreases in IGF-1 and tibial bone mass at 7–14 days postinjury. RTBI during adolescence in females could negatively impact hormones involved in growth and development of the skeletal system.

GENDER

Although the majority of TBI research has focused on male animal models, epidemiological studies show an increase in the number of females experiencing concussions and RTBI. The incidence of sports-related concussions and repeat concussions have increased annually since 1997 in teens and young adults[1] with many sports showing greater incidence of head injury among female athletes.[33–35] Although this issue is of growing public concern, to date, only two research studies have addressed RTBI in a female adolescent animal model.[30,36] The same repeat CCI injury model discussed in the previous sections was used to study memory and social interaction in the female adolescent rat.[36] Unlike the males, adolescent female rats failed to perform the novel object task. It has been previously demonstrated that females at this age show gender differences in preferences for novel objects.[37] This emphasizes the importance in taking gender differences into account when studying the effects of TBI. Females with four RTBI at 24-hour intervals did show significant decreases in total social time, number of times play was initiated, and times play fighting with novel females with increase in play avoidance. These results demonstrate that repeat concussions could have significant impact on adolescent female social interaction, which can contribute to quality of life during a period of dynamic cerebral development.

CHRONIC PATHOLOGY

Another WD model has also been applied to PND35-42 mice to examine the effects of RTBI on chronic pathology.[29] After establishing that a 40-g weight released from 1 m produced a mild injury, one impact or three impacts per day were given at 0, 1, 3, and 7 days. The magnitude of axonal injury increased with number of injuries in the optic tract, cerebellar lobule, and corpus callosum at 7 days postinjury. Density of microglia cells also increased with injury number at 7 days after injury, which returned to sham levels at 10 weeks postinjury. No phospho-tau immunoreactivity was detected in this model. This model produces detectable changes in axonal injury with RTBI in the visual system and cerebellum that can be used to examine adolescent TBI therapeutic interventions.

Prepubertal repeat TBI

CHARACTERIZATION OF PATHOLOGY TIME COURSE

In contrast to the adolescent age group, RTBI models have also been applied to younger postnatal age groups to examine age-related differences in outcomes. Modification of the CCI injury model impactor tip to include a 9.5-mm rubber end was used on an exposed skull in postnatal day (PND) 18 rat pups to give one, two, or three injuries at 24-hour intervals to examine early and chronic histology and behavioral outcome measures.[31] A single mTBI produced axonal degeneration, but no behavioral assessments were done in this group. Evidence of axonal injury was greater in RTBI groups with increased microglial reactivity at 7 days postinjury. No differences between sham and RTBI groups in beam balance, Morris water maze (MWM), or elevated plus maze (2 weeks, 2 months), but impairments were present in novel object recognition (18 days) and fear conditioning tasks (day 92 postinjury).

A modified WD model was used to address gross pathological changes after RTBI in the prepubertal brain. PND20 rats were positioned on a taut Kimwipe™ during the impact of a 92-g weight dropped from 865 mm, allowing the animal to freely move upon impact.[32] In this model, the effects of a single injury were not characterized, and the RTBI group of five injuries at 24-hour intervals was compared to sham animals. At 14 days postinjury, MRI analysis revealed cortical thinning at the impact site, ventriculomegaly of the lateral ventricles, and Neu-N staining showed neuronal loss within the motor cortex after RTBI. Among the models discussed thus far, the pathology in this animal model is more severe.

REPEAT MILD TBI IN ADULT ANIMAL MODELS

Metabolism

A hallmark characteristic of all types of TBI includes acute and long-term alterations to cerebral metabolism. It has been well characterized after experimental and clinical

brain injuries that glucose metabolism increases immediately after injury transiently, followed by a prolonged period of cerebral glucose metabolic depression.[38] Changes in cerebral metabolism, blood flow, and vascular responsiveness have been recently addressed in models of RTBI (Table 3.2). WD (Kimwipe) injury of five impacts (24-hour interval) delivered to adult mice produced significant decreases in cerebral blood flow that did not recover until 3 days postinjury along with MWM performances.[39] A single impact showed CBF recovery within 24 hours after impact. These findings are consistent with the impairments in vascular reactivity observed after repeat WD in the adult rat.[40–42] A cranial window was used to measure cortical vascular response to acetylcholine application after RTBI at various intervals (3, 5, or 10 hours). A single injury showed no impairment in vascular response to acetylcholine application, but after two injuries at 3-hour intervals, failure of vessels to vasodilate was observed. The vascular reactivity impairment decreased with greater intervals between injuries with 10-hour interval groups responding similarly to single and sham animals. The axonal injury burden followed the pattern of impaired microvessel reactivity, and both measures were improved with animals that were treated with FK506 and hypothermia.[41,42]

These RTBI-induced acute changes in cerebral vascular responses occur simultaneously with markers of metabolic crisis and oxidative stress. RTBI with the Marmarou WD model in adult rats at various intervals showed that the interval between injuries directly affected the decreases observed in metabolic markers (ATP, NAA, NAD, and acetyl CoA) and increases in oxidative stress (malondialdehyde, glutathione, nitrite).[43,44] Maximal impairments occurred with injuries that were given at 3-day intervals, and with 5-day injury intervals, the markers reflected sham levels. Injury interval was also related to changes in cerebral glucose metabolism after RTBI in adult mice.[45] A lateral WD injury was used to deliver one or two injuries at 3-day or 20-day intervals, and CMRg was quantified with ^{14}C-2DG autoradiography at 3, 6, and 10 days after the last injury. The cortical pattern of CMRg differed from previously reported patterns of change with increases in CMRg observed at 6 days after a single injury followed by prolonged metabolic depression. It is unclear if this difference can be attributed to species response differences or the lateral nature of this WD injury model. Injuries given at 3-day intervals did not show significant changes from sham animals, but those with impacts at 20-day intervals showed cortical CMRg increases at 6 days after the last injury. Collectively, these acute studies demonstrate that many of the early cascades that are initiated following moderate and severe injuries are present after repeat mild injuries and that the interval between injuries directly affects the magnitude of accumulating impairments.

Inflammation

Another cascade that is well characterized after TBI is the evidence for inflammatory responses. Moderate and severe TBI both cause significant morphological changes in astrocytes and microglia as well as increases in cytokines.[46] Single mild brain injuries produced by either CCI or WD models generally produce small increases in astrocytosis and microgliosis during the first week in cortex, hippocampus, corpus callosum, or cerebellar regions in the absence of cell loss[47–49] (Table 3.3). It is important to note that there are some unique features among the models reported in Table 3.3 that should be considered. Huang[48] and Aungst[50] both use modified injury models that produced cell loss with a single impact that increase with increasing number of injuries. Cell loss and contusions are not pathologies that are commonly seen among single or repeat concussions and may reflect a greater severity of these models. Another consideration between studies is the type of anesthesia. The majority of studies utilize isoflurane, but several use pentobarbital prior to injuries, which can cause significantly greater metabolic depression than inhaled anesthesia. Interestingly, Petraglia and colleagues[49] is the only study, thus far, to report a repeat injury model conducted with no anesthesia while the animal is held in a restraint cone. Despite the differences in models used, number of injuries, and interval between injuries, RTBI given at shorter intervals produced greater increases in reactive astrocytosis and microgliosis during the first postinjury week, and evidence of chronic inflammatory responses (2–6 months) has also been observed.[49,51–53] The long-lasting nature of the inflammatory response to RTBI suggests a role in exacerbation of axonal injury, synaptic dysfunction, and development of neurodegenerative diseases.

Axonal injury

Clinically, concussions are usually both CT and MRI negative, but subtle axonal disconnections could be used to characterize mTBI. Axonal injury has been assessed in many of the RTBI models presented (Table 3.4). A modified CCI injury was used to deliver a single or two injuries at 24-hour intervals to 2- to 3-month-old mice.[51] The single mTBI group showed no gross neuronal loss, no APP staining, or MWM deficits. RTBI animals showed MWM deficits during the first week with partial recovery by 7 weeks postinjury with evidence of corpus callosum injury, few APP staining and positive reactive microgliosis at 7 weeks postinjury. This study was followed by the use of diffusion tensor imaging (DTI) in combination with immunohistochemistry techniques to assess the time course of axonal injury.[54] No changes in DTI were detected at 24 hours. There were significant decreases in axial and mean diffusivity in white matter that correlated with silver staining, but not APP, at 7 days. Application of the same injury paradigm to a CD11b-TK knockout mouse with reduced microglial population did not alter the degree of axonal injury with RTBI,[55] suggesting that microglia may not contribute to axonal injury. In addition to the closed head CCI injury model, the FP injury model has also been used to address cytoskeletal changes after repeat injuries in the adult rat.[56]

Table 3.2 Adult animal models of repeat TBI: Vascular and metabolic responses

Type	Age/species	Injuries specifics	Injury parameters	Anesthesia	Outcome measures	Single injury	References
WD (Kimwipe)	Mouse adult	54 g at 38 in	One or five impacts/24-h interval (pentobarbital)	Isoflurane	Cerebral blood flow	Yes	Buckley et al.[39]
WD (Marmarou)	Rat adult	450 g at 0.5, 0.75, or 1 m	Two impacts/3-, 5-, or 10-h intervals	Pentobarbital	Vascular reactivity	Yes	Fujita et al.[40]; Miyauchi et al.[41,42]
WD (Marmarou)	Rat adult	450 g from 1 m	Two impacts/1-, 2-, 3-, 4-, or 5-day intervals	Halothane/ Propofol	Markers of metabolic crisis and oxidative stress	No single injury	Vagnozzi et al.[43]; Tavazzi et al.[44]
WD (lateral)	Mouse adult	37 g from 15 cm	One or two impacts/3- or 20-day intervals	Isoflurane	Cerebral glucose metabolism	Yes	Weil et al.[45]

Table 3.3 Adult animal models of repeat TBI: Inflammatory responses

Type	Age/species	Injuries specifics	Injury parameters	Anesthesia	Outcome measures	Time postinjury	References
CCI	Mice adult	5-mm tip silicone, 2-mm depth, 3.5 m/s, restrained, skull exposed	One or five injuries (1- or 2-day intervals)	Isoflurane	Reactive astrocytes and microglia in hippocampus, entorhinal cortex, cerebellum	1 day, 5 days, 9 days	Bolton and Saatman[47]
CCI	Rat adult	4-mm tip, 0.5-mm, 6 m/s, restrained, skull exposed	Two injuries (1-, 3-, or 7-day intervals)	Isoflurane	Reactive astrocytes and microglia in cortex. *Single injury causes cell loss.	7 days	Huang et al.[48]
CCI	Mice adult	5-mm tip, 1 mm, 5 m/s, closed skin, light restraint	One or five injuries/48-h interval	Isoflurane	Reactive astrocytes and microglia	1 day, 6–18 months	Mouzon et al.[57,58]
CCI	Mice adult	6-mm rubber tip, 1 cm, 5m/s, cone restrained	Six impacts/24-h interval	None	Reactive astrocytes and microglia	7 days, 6 months	Petraglia et al.[49]
FP	Rat adult	4-mm craniotomy, lateral	Three impacts/2-day interval	Isoflurane	*Single injury causes cell loss, Reactive microglia in cortex	1 month	Aungst et al.[50]
CCI	Mice adult	9-mm rubber tip, 3.3 mm, 5 m/s, restrained, skull exposed	One or two impacts (24-h interval)	Isoflurane	Reactive microglia, silver staining	2 months	Shitaka et al.[51]
WD (Kimwipe)	Mice adult	54 g from 28 in.	Seven impacts in 9 days	Isoflurane	Reactive astrocytes and microglia	3 months	Mannix et al.[52]
CCI	Mice adult	9-mm rubber tip, 3 mm, 3–5 m/s, restrained, closed skin	Three impacts/24-h interval	Isoflurane	Reactive astrocytes, cortex, CA3, corpus callosum	6 months	Luo et al.[53]
FP	Rats adult	3-mm craniotomy, lateral	One, three, or five impacts/5-day interval	Isoflurane	Elevated plus maze, MWM, open area, balance beam, forced swim test	1–3 days, 2 months	Shultz et al.[59]

Table 3.4 Adult animal models of repeat TBI: Axonal injuries

Type	Age/ species	Injuries specifics	Injury parameters	Anesthesia	Outcome measures	Time postinjury	References
CCI	Mice adult	9-mm rubber tip, 3.3 mm, 5 m/s, restrained, skull exposed	One or two impacts (24-h interval)	Isoflurane	APP and silver staining	2 months	Shitaka et al.[51]
CCI	Mice adult	9-mm rubber tip, 3.3 mm, 5 m/s, restrained, skull exposed	Sham, two impacts/24-h interval	Isoflurane	DTI imaging, APP staining	1–3 weeks	Bennett et al.[54]; Bennett and Brody[55]
FP	Rat adult	1 atm, lateral	Seven impacts/24-h interval	Pentobarbital	MAP2, neurofilament staining	1 week, 1 month	Kanayama et al.[56]
CCI	Mice adult	9-mm rubber tip, 3 mm, 5 m/s, restrained, skull exposed	Sham, one or two impacts/3-, 5-, 7-day intervals	Isoflurane	APP staining	1 week	Longhi et al.[60]

At 1 week postinjury, microtubule-associated protein 2 and phosphorylated neurofilament proteins accumulated in the neuronal perikarya and dendrites. After 1 month, these protein accumulations increased further, and tau-1 immunoreactivity was detected in the cell bodies. Increasing the interval between injuries has been shown to decrease the degree of axonal injury observed. CCI injuries given to adult mice at 3-, 5-, or 7-day intervals showed increases in APP labeling in axons in the corpus callosum, hippocampus, thalamus, and hypothalamus during the first week.[60] The RTBI 3-day interval showed a greater number of injured axons than those animals with injuries at 7-day intervals. These indicators of early cytoskeletal disruption indicate ongoing impairment of axonal transport after RTBI.

Acute and chronic behavioral profiles

The clinical presentation of concussions and mTBI include transient functional impairments in the absence of gross pathology. The balance between generating animal injuries that produce minimal pathology with an injury that produces detectable functional impairments has been a great challenge for experimental model development. Functional deficits within the first week postinjuries have been easier to detect. Several studies have characterized the effects of multiple impacts on acute behavioral function (Table 3.5). Adult mice were given one, three, five, or 10 concussions with the modified WD (Kimwipe) model at 24-hour intervals to examine the effects of cognitive performance 1 day after these injuries.[61] Animals with a single injury had MWM escape latencies similar to sham animals, but the cognitive deficits increased with the number of concussions. A separate group of animals with five concussions at 24-hour, 1-week, 1-month, or 1-year intervals were examined to determine the impact of injury interval on cognitive performance at 1 day post last injury. Consistent with other injury interval studies, animals with injuries sustained at 24-hour or 1-week intervals showed the greatest cognitive impairments when tested 1 day postinjury and continued to show deficits at 1 year postinjury, even without histological pathology. Similar results were obtained with the modified CCI injury in adult mice.[60] The magnitude of impairments in spatial learning and vestibulomotor function increased with the number of injuries and decreased with greater intervals between injuries (3- and 5-day intervals). RTBI generated with a WD injury also revealed delayed righting times and impaired MWM performance (5 days postinjury) but demonstrated ventral cerebral cell loss.[62] In the absence of cell loss or blood–brain barrier compromise, a modified WD injury in mice (four impacts/24-hour interval) resulted in significant spatial learning deficits 1 week postinjury in the MWM.[63] These studies of the acute effects of RTBI on behavioral function consistently demonstrate the cumulative nature of multiple concussions on cognitive impairments and that the interval between injuries directly affects this outcome measure.

These RTBI models have also been used to address the question of the enduring nature of these behavioral impairments. MWM, novel object recognition, and Barnes maze impairments were detected during the first month after repeat FP impacts,[50,59] repeat CCI injury,[48] and repeat frontal CCI.[64] Adult rats with repeat CCI injuries did not show MWM deficits when the injury interval was increased to 20 days.[65] Manipulation of these deficits at 1 month postinjury with chronic alcohol did not improve MWM performance,[66] but reduction in the tau allele of the transgenic mouse model prevented spatial learning and memory deficits.[64] Reports of chronic impairments in MWM latencies 3–6 months after injury were characterized after repeat WD (Kimwipe).[49,52,53]

Table 3.5 Adult animal models of repeat TBI: Behavioral responses

Type	Age/species	Injuries specifics	Injury parameters	Outcome measures	Postinjury time	References
WD	Mice adult	21 g from 35 cm	Three impacts/24-h interval, no single group	Righting, activity, sensorimotor, MWM (cell loss present)	5 days pid	Creeley et al.[62]
WD (Kimwipe)	Mice adult	54 g from 38 or 42 in.	One, three, five, 10 impacts/24-h, 1-month, 1-year intervals	MWM	1 day pid	Meehan et al.[61]
CCI	Mice adult	9-mm rubber tip, 3 mm, 5 m/s, skull exposed, restrained	One or two impacts/3-, 5-, 7-day intervals	MWM, rotorod	1 day pid	Longhi et al.[60]
WD	Mice adult	50, 100, or 150 g from 40 cm	Four impacts/24-h interval	MWM	14 days	DeFord et al.[63]
FP	Rat adult	4-mm craniotomy, lateral	Three impacts/2-day interval	MWM, novel object recognition, single injury causes cell loss	14–21 days	Aungst et al.[50]
CCI	Rat adult	4-mm tip, 0.5 mm, 6 m/s, restrained, skull exposed	Two impacts/3-day interval	Exploratory behavior and MWM, single injury causes cell loss	1 month	Huang et al.[48]
CCI	Rat adult	Silicon tip, 3 mm, 5 m/s	Sham, one, or two impacts (20-day interval)	MWM	14 days	Gurkanlar et al.[67]
FP	Rat adult	6-mm craniotomy, lateral	Three impacts/4-day interval	Reflex, MWM	3 weeks	Biros et al. 1999[66]
Frontal CCI	Mice adult	56-g ball, impacts frontal cortex	Two impacts/? interval	Barnes maze, Y maze, fear conditioning, elevated plus maze, open field, balance beam	1 month	Cheng et al. 2014[64]

Table 3.6 Adult animal models of repeat TBI: Neurodegenerative diseases

Type	Age/species	Injuries specifics	Injury parameters	Outcome measures	Single injury	References
CCI	Tg mouse adult	6- to 9-mm rubber tip, 1-mm depth, 4.8 m/s velocity, restrained, skull exposed	Two to four injuries/24-h interval (pentobarbital)	Neurodegenerative disease at 2–6 months postinjury	Yes	Laurer et al.[68]; Uyru et al.[69]; Yoshiyama et al.[70]; Conte et al.[71]
CCI	Mouse 6–10 weeks	3-mm tip, 2.2-mm depth, 3 m/s velocity, restrained, skull exposed	Three injuries/24-h interval	Neurodegenerative disease at 7 days and 1 month postinjury	Yes	Zhang et al.[72]
CCI	Htau Tg mice adult	5-mm tip, 1-mm depth, 5 m/s, Restrained, no incision	One or five impacts/48-h interval	Phosphotau expression and inflammatory response at 3 weeks	Yes	Ojo et al.[73]
FPI	Rat adult	1 atm	Seven injuries/24-h interval (pentobarbital)	Tau expression at 1 week, 1 month	?	Kanayama et al.[56]

Neurodegenerative diseases

A modified CCI injury was characterized in adult mice to examine the effects of RTBI on neurodegenerative diseases in subsequent studies (Table 3.6).

Adult mice received sham, single, or two impacts 24 hours apart and were behaviorally assessed prior to histological evaluation.[68] A single mild injury produced transient neuroscore deficits at day 3, but no MWM impairment and mild histopathology, including cortical blood–brain barrier disruption and focal axonal injury. The RTBI group showed no cognitive deficits but greater impairment on all outcome measures than single impact. The C57BL/6 mouse did not show Aß deposition or tau immunoreactivity, and, thus, the injury parameters were applied to a transgenic mouse model. AD transgenic mice (Tg2576) were given sham, single, or two injuries at 24-hour intervals at 9 months of age, and Aß deposition was quantified at 2 days and 9 and 16 weeks postinjury.[69] A single injury did not increase Aß expression. RTBI increased Aß deposition, increased cognitive deficits and greater oxidative stress at 16 weeks. Animals that were supplemented with vitamin E for 4 weeks prior and 8 weeks after RTBI showed significant reduction in lipid peroxidation and Aß deposition.[71] This finding suggested a link between the oxidative stress and amyloid accumulation after RTBI. This injury model was also applied to 12-month-old T44 tauopathy transgenic mice[70] with four impacts in 1 day, once a week, for 4 weeks. Behavior at 6 months postinjury did not show deficits in the RTBI group and at 9 months showed increased neurofibrillary tangles and cerebral atrophy. Increases in phospho-tau expression were also seen at 1 month after three repeat injuries (24-hour interval) in the nontransgenic mouse.[72] Treatment with monoacylglycerol prior to the injuries decreased the tau expression and inflammatory responses and improved markers of plasticity and cognitive performance. Collectively, these studies demonstrate that RTBI can increase the progression of neurodegenerative pathologies in those predisposed to the disease.

SUMMARY

The growing concern about the effects of RTBI has prompted the development of numerous experimental models. Many of these models have characterized mild injuries with detectable transient behavioral deficits with minimal pathology. Collectively, the experimental research has, thus far, revealed that 1) multiple concussions have cumulative affects and 2) brain impact interval matters. Clinical data has reported that multiple concussions decrease rate of information processing;[74] cause slow recovery of balance deficits;[8] increase learning disabilities;[6,75–77] and increase difficulties with memory, concentration, and headaches.[75] The experimental models in adolescent and adult animal models show that the greater the number of impacts, the greater the magnitude of impairments. Additionally, as the time between impacts increases, the magnitude of impairments is minimized. This finding reinforces the need to respect return-to-play guidelines to reduce cumulative deficits. These experimental models of RTBI will be essential in determining *age-specific* methods to image concussions, determine biological markers for safe return-to-play guidelines, treatments to improve outcomes in those with chronic postconcussive symptoms, and treatments to minimize risks for neurodegenerative diseases.

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4

Neuroplasticity and rehabilitation therapy

ROBERT P. LEHR, JR.

INTRODUCTION

The skilled therapist of the brain-injured person requires an understanding of the underlying anatomy and physiology, its relationship to the injury, the mechanisms of learning, and the creative array of multimodal therapeutic skills that he or she has at his or her disposal. The twenty-first century brings an ever-increasing understanding of the mechanisms involved in how the brain accomplishes learning and how these mechanisms are impacted by the traumatic event. We are at a point at which we must view more than just the injury to the neurons and must consider the damage to the environment in which the neurons exist. This chapter reviews some of these issues and provides some insight into the therapeutic process.

Therapies are what have been described as being activity-dependent.[1] Being activity-dependent means the therapy is focused to the point that the recipient of the therapy is actively engaged in the therapeutic process. Therapies are designed by the therapist to elicit a key response from the client, and this leads to one part of a successful rehabilitative program. Learned skills have their foundation in the nervous system, and we now know that there are physical changes that take place at the synaptic level to produce the rehabilitative results. It is the synaptic environment that is the ultimate target of the therapeutic process. The purpose of this chapter is to provide therapists with a better understanding of neuronal changes and how the human brain is altered by their therapies.

Neuroplasticity refers to the ability of the brain to change its structure and organization as the organism encounters its environment.[2] The human brain is composed of a collection of neurons that have been shown to be pliable and subject to changes in structure, individually as well as collectively, if the interaction between them is initiated with purposeful intent. Just because the brain is active does not mean it is learning. Learning comes from purposeful activity in which the learner is fully participating. As you will recall, just sitting in the classroom did not guarantee the acquisition of the material of the lecture. It was not until you actively studied the material, committed it to memory, or put it to use that you learned the material. In a like manner, the traumatic brain injury (TBI) client must be committed and actively engaged in the therapeutic process.

Now to look at some of the learning processes therapists initiate and see them on the cellular level. It is hoped that this insight will stimulate in the reader a better appreciation of the processes involved and perhaps lead to some innovative therapies.

The early prediction by Hebb[3] that there would be observable changes in the neurons or their synapses was further elaborated by neuroscientists to suggest that the behavioral changes an organism makes in response to the influences of the environment would be reflected in changes in synapses in the central nervous system.[4] Neurobiologists (Bailey and Chen,[5] Kandel,[1] and others) followed with elegant experiments that demonstrated the importance of this synaptic organization and the interactions that occur between the neurons and, as we will see later, the supporting glia. Using very simple animals, such as marine snails and moving on to rodents and mammals, these investigators were able to clarify the role of the synapse in learning.

Learning is a complex process that has several levels. We look at learning in terms of habituation, sensitization, classical conditioning, and operant conditioning. These are by no means the only concepts involved in learning, but they

allow us to illustrate some changes that take place in the cellular organization of the brain and to place them in the context of therapy.

HABITUATION

Kandel,[1] using the California marine snail *Aplysia*, has demonstrated the simple form of learning known as *habituation*. This form of learning is characterized by the reduced response to a presentation of a novel stimulus. The experimental setup is demonstrated in Figure 4.1. When a stimulus is applied to the siphon, the snail responds by reflex withdrawal of its gill, mantle, and tail. With repeated stimulation to the siphon, there is a depression of the reflex response. The decreased response is characterized by a decrease in the synaptic transmission from the presynaptic sensory neurons to the interneurons and motor neurons in the reflex circuit (Figure 4.2). There is a decrease, over time, of the amount of transmitter released. These changes are internal to the presynaptic neuron and can last for a few minutes or a few hours. This is known as *short-term habituation*.

When stimulation occurs over several training sessions, there has been demonstrated an actual reduction in the number of synapses present to the postsynaptic neuron, and this process is known as *long-term habituation*. Although this has not been demonstrated in humans, it can be speculated that this is what occurs when we condition a client who has symptoms of dizziness by constant exposure to a revolving swing. The constant presentation of a stimulus that produces the dizziness will, in time, habituate. First, there is a reduction of neurotransmitters and then, eventually, a reduction of synaptic connections so that a stable equilibrium may be obtained without nausea.

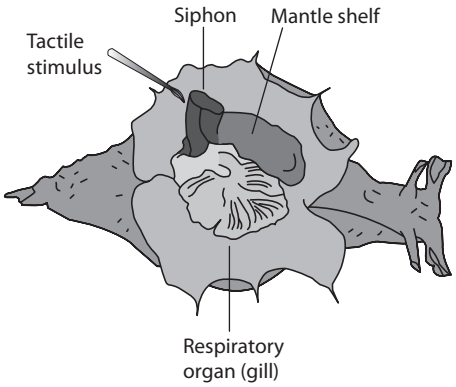

Figure 4.1 Marine snail *Aplysia*: experimental setup. (From Kandel, E. R., Cellular mechanisms of learning and the biological basis of individuality, in *Principles of Neural Science*, 4th ed., Kandel, E. R., Schwartz, J. H., and Jessell, T. M., Eds., McGraw-Hill, New York, 2000, p. 1248. Used with permission.)

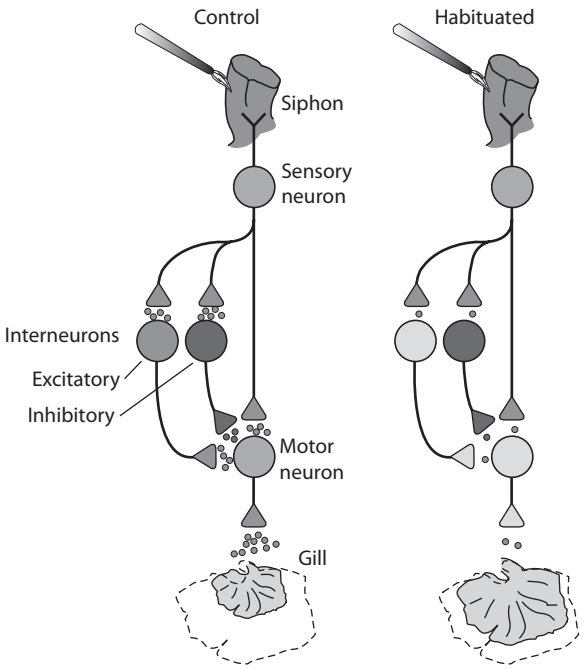

Figure 4.2 Marine snail *Aplysia*: gill-withdrawal reflex circuit. (From Kandel, E. R., Cellular mechanisms of learning and the biological basis of individuality, in *Principles of Neural Science*, 4th ed., Kandel, E. R., Schwartz, J. H., and Jessell, T. M., Eds., McGraw-Hill, New York, 2000, p. 1248. Used with permission.)

SENSITIZATION

In *sensitization*, the process involves an additional neuron and is more complex. The additional neuron is one that "facilitates" the signal by reinforcement (see Figure 4.3). It is an enhancement of the reflex response after the presentation of a strong stimulus. After a strong stimulus, the organism is more attentive to all stimulations to itself and the nature of the synapse physically changes.[1] There is an increase in the size of the synaptic zone[1] (Figure 4.4) and in the number of vesicles containing neurotransmitters in the active zone.[7] These changes in the circuit demonstrate that there is a "memory" of what has happened to them. These changes last several minutes and are known as *short-term sensitization*.

Long-term sensitization also occurs following several training sessions (Figure 4.4). This process produces proteins that enhance the short-term mechanisms and also promotes the growth of axons with new synapses. These newly produced proteins have been shown to be persistently active for up to 24 hours without requiring a continuous signal of any sort. This is an exciting opportunity for the therapy regimen. These new synapses cause the postsynaptic neuron to increase its dendritic branches to accommodate the new synapses from the axons of the presynaptic neurons.[7]

Recent research by Fellin, Pascual, and Haydon[8] has demonstrated the active role of the glial astrocyte in the

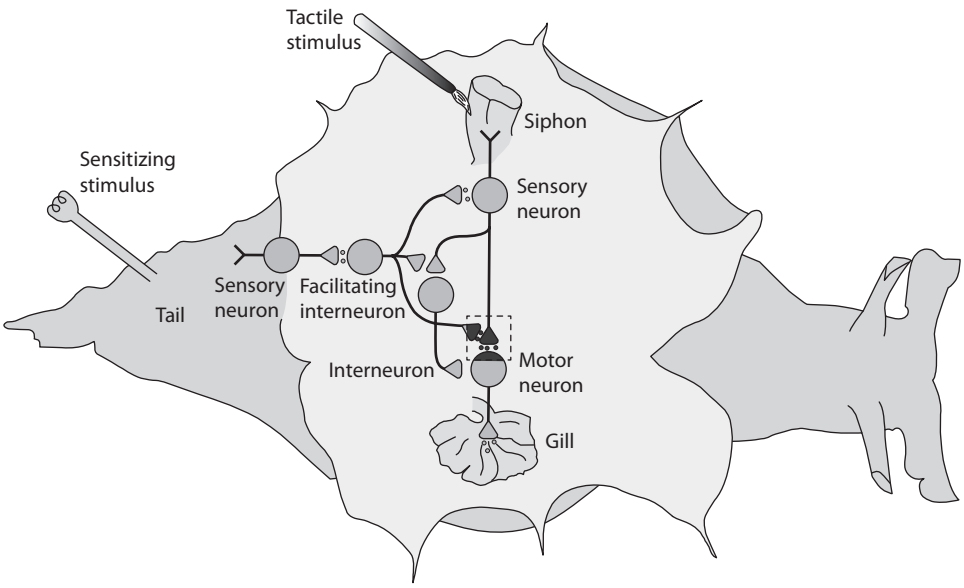

Figure 4.3 Marine snail *Aplysia*: gill sensitization. (From Kandel, E. R., Cellular mechanisms of learning and the biological basis of individuality, in *Principles of Neural Science*, 4th ed., Kandel, E. R., Schwartz, J. H., and Jessell, T. M., Eds., McGraw-Hill, New York, 2000, p. 1251. Used with permission.)

coordination of the synaptic processes. Although the details of the exact role of this interaction have not been clarified, there is evidence of a feed-forward as well as a feedback modulation of the activity at the "tripartite" synapse (Figure 4.5).

This synaptic plasticity is "activity-dependent" and, with the increased axonal sproutings, increased neurotransmitters, and correspondent dendritic field expansion, there are changes in the surrounding tissue. There are increases in the glial cell components and an increase in the vascular supply to the region. These changes are rapid and have been identified to take place within 10 to 15 minutes.[9] The therapist must move quickly to reinforce the target behavior when the client demonstrates the acquisition of that sought behavior.

Additionally, exercise has been demonstrated to increase the number of synapses in the cerebellum of experimental animals that undergo complex motor skill learning but not mere motor activity.[10] These demonstrations of the plasticity of the brain at the cellular level show that a new foundation for the behavior has been formed, and the repetition of the behavior will reinforce the newly formed synaptic connection. As we repeat the activity in a therapy setting, we increase the effectiveness of the corresponding synapses, and this, in turn, contributes to the reacquisition of the skills.

TYPES OF LEARNING

Learning and memory are closely associated and sometimes difficult to separate except for academic purposes. For the therapist, however, they are intertwined in a more specific way. The rehabilitation process involves the returning to wholeness of the entire person and, as such, makes demands on many systems, from the locomotor to the cognitive. The cellular mechanisms involved in the learning and memory processes we are discussing are the same. The two types of learning we discussed earlier, habituation and sensitization, are forms of *nonassociative* learning with which the organism learns the properties of a single stimulus.

In another form of learning, *associative*, the organism learns about the relationship between two stimuli or between a stimulus and a behavior.[11] For the therapist, it might be more productive to view the learning–memory process as being based on the classification of *explicit* and *implicit* memory. It is not our purpose to engage in an extensive discussion of memory but to set the stage for the learning process within the therapeutic setting.

Explicit memory deals with facts and events. This form of memory is recalled by a deliberate conscious effort. Facts and remembering events are the purview of the entire rehabilitative team. It is also the area in which the cognitive functions of the skills of daily living are rehabilitated. The skills to plan the day, to shop for groceries, and to make change for a dollar are some of the items of concern, and these require the reestablishment of the explicit memory.

Explicit memory has been shown to involve *long-term potentiation* (LTP) in the hippocampus. In fact, the presence of LTP in the hippocampus was the first confirmation of Hebb's rule that learning would be based in the physical changes in the synapse. LTP represents the receptiveness and increased facilitation of the excitatory synaptic potentials in the postsynaptic neurons that can last for hours, weeks, or months.[7] The relationship, in time, of two presenting stimuli increases the efficacy of the two synaptically related cells and is a reminder to the cells of that relationship.

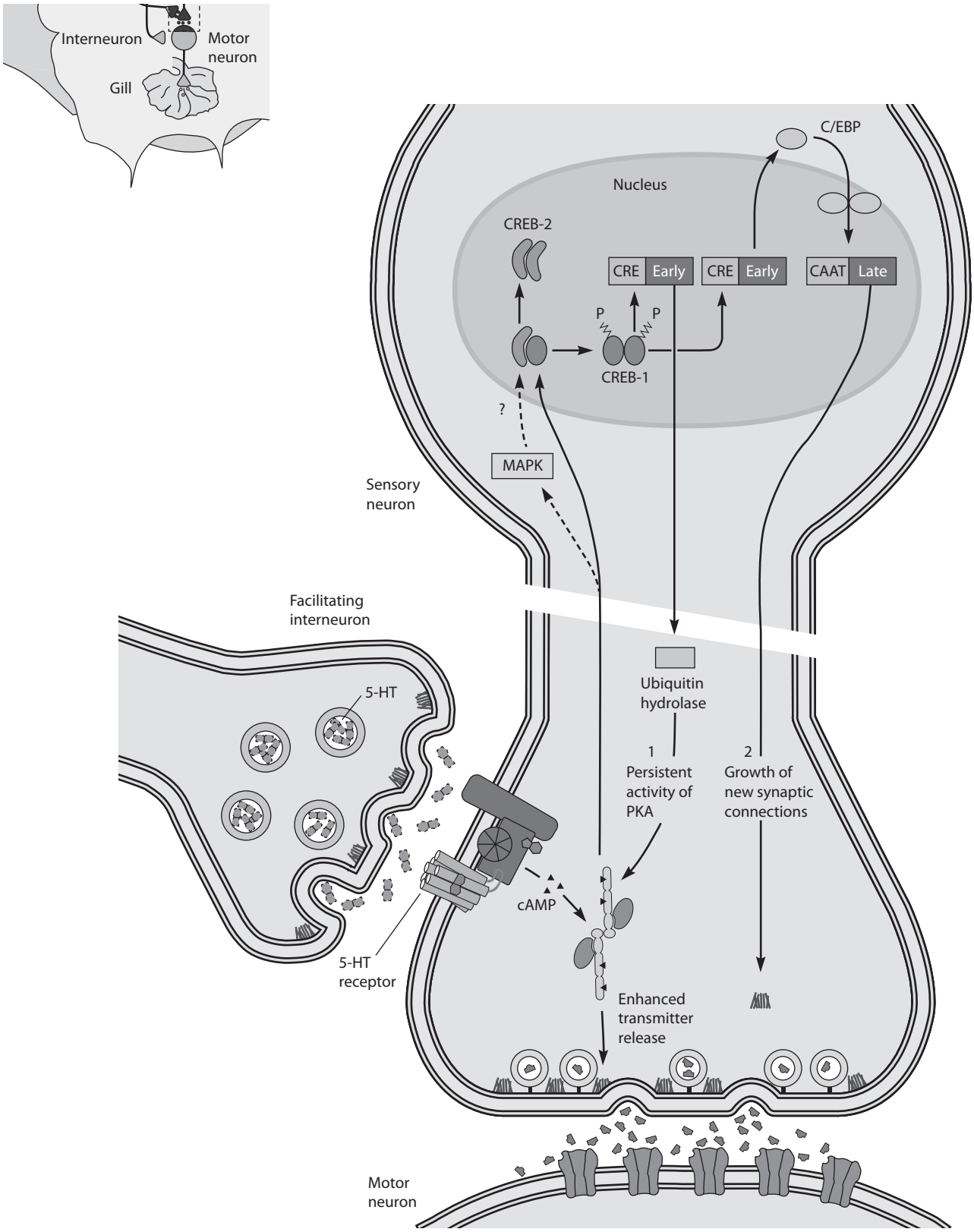

Figure 4.4 Schematic model for short-term enhancement and persistent synaptic enhancement with long-term sensitization. (From Kandel, E. R., Cellular mechanisms of learning and the biological basis of individuality, in *Principles of Neural Science*, 4th ed., Kandel, E. R., Schwartz, J. H., and Jessell, T. M., Eds., McGraw-Hill, New York, 2000, p. 1255. Used with permission.)

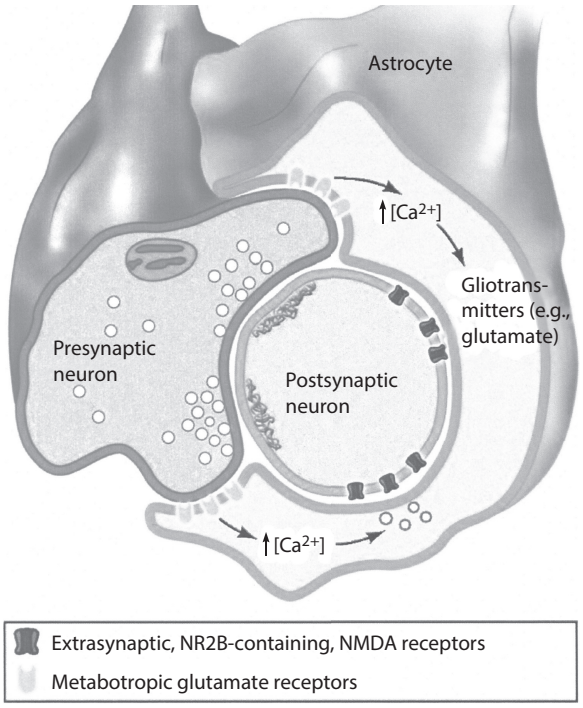

Figure 4.5 Schematic representation of the glial astrocyte in the coordination of the synaptic processes. (From Fellin, T., Pascual, O., and Haydon, P. G., Astrocytes coordinate synaptic networks: Balanced excitation and inhibition, *Physiology*, 21(3), 208–215, 2006. Used with permission.)

This synaptic enhancement can take different forms in different parts of the hippocampus. Recent research has shown that the hippocampus is a key component in early memory and in the final distribution of information to the multimodal association areas of the cerebral cortex. The left hippocampus seems to be involved with verbal memory, whereas the right hippocampus seems to be more involved with the representation of the environment and the ability to find our way in it.[7] Suffice it to say that the association of the hippocampal and multimodal association cortical neurons and their associated astrocyte cell support is established in the synapses of their respective neurons.[8] The reinforcement with repeated practice is what produces a successful therapeutic regimen.

Implicit memory, on the other hand, refers to how to perform an act. These memories of a specific task do not require conscious effort to recall or to reestablish. They require concentration and a focus on the task at hand but not the conscious effort of recall. Implicit memory is seen in the training of skilled movements and perceptual skills. These are the skills of walking, driving a car, or performing other motor tasks.[7]

Implicit memories involve habituation and sensitization, and they also include two other processes, *classical conditioning* and *operant conditioning*. These processes involve the concept of association. In classical conditioning, there are two stimuli presented, which, after a series of associations with each other, begin to produce a new response. These associations are established in the synapses of the cooperating neurons. This new response then enables the organism to predict the environment.

In operant conditioning, the associative relationship is between the organism and a subsequent behavior produced. The organism learns that, for a specific action, there is a related reward. Thus, if behavior is controlled, then the individual receives an appropriate reward for that action. This is the foundation for the wide use of behavioral modification programs (see Chapter 25 by Persel and Persel).

Classical conditioning relies on an association in which a stimulus that had been previously incapable of producing a response is paired with a strong stimulus that does produce the response, and the association between the two will eventually produce the response from the weaker stimulus. Classical conditioning results in a greater and longer-lasting enhancement. This process is one in which there is a presynaptic facilitation of the synaptic transmission. It is the pairing, in time, of a meaningful relationship that produces the result. The internal mechanisms of the process are solidly established and involve several enzymes and genes.[7] The combinations of enzymes and genes are the same as we saw in the process of long-term sensitization. The production of the cellular proteins by this process forms the foundation for the results seen in the therapeutic program.

HIERARCHICAL LEARNING

Rehabilitation, as a process, requires the work of several respective professions. Among these, the professions of physical and occupational therapy hold, as a major tenet, the developmental concepts in neurodevelopmental theory.[12,13] Neurodevelopmental theory says that there is a basic developmental sequence in the individual from the time of conception to adulthood. The function that is expressed is built on previously learned foundations. We must crawl before we walk. Therefore, it is important that the process of restoration of function should follow the same sequences that occurred in development.

Kandel's group[1] has shown that the stages of learning mentioned above are sequential. The infant *Aplysia* is first capable of only habituation; then, with maturity, dishabituation occurs and, finally, sensitization. These sequential stages of learning confirm that learning is a process that builds on previously developed mechanisms and is not complete at birth. This understanding seen in the simple snail lends support to the foundation of some long-standing therapies of rehabilitation[3,4] that suggest a hierarchy exists in the development of the individual, and successful therapy must be carried out in the same order.

It is clear that learning is a hierarchical process and has a neuronal basis. It is not so clear in the cognitive area in which we have only begun to investigate the cognitive functions with modern imaging techniques and cellular neurophysiological experiments. The literature on cognition is rich, indeed, and has provided a foundation of strategies that has been successfully incorporated into

the rehabilitation environment (see chapter in this text by Constantinidou et al.).

Cognitive scientists tell us that we are first able to describe objects using very simple descriptions of color, size, and shape. From this base, we can move to the descriptions of their usefulness and, eventually, to the features of the object, allowing use of the object for other extended purposes.[14]

Current concepts in the neural sciences are beginning to reveal a neural concreteness to constructing the visual image from the features of the object. The neural pathway for vision is known to have two parallel pathways that convey different types of information.[15] One pathway, the P pathway, is concerned with form, size, and shape or *what* the object is. The P pathway projects to the temporal multimodal association cortex. The other pathway, the M pathway, is concerned with movement and depth perception or *where* the object is located. This M pathway projects to the parietal multimodal association cortex.

As these two pathways project to separate areas of the cerebral cortex, this helps explain the selective loss of some features of an object. As an example, object agnosia, the ability to name an object, is associated with Brodmann areas 18, 20, and 21 on the left temporal cortex, whereas color anomia, the ability to name a color, is associated with the speech zones or connections for Brodmann areas 18 and 37. The mechanism of the complete visual construct is pulled together by a yet unknown *binding mechanism*.

The binding mechanism takes the properties of form (rectangle), color (yellow), and dimensions in depth (box), and says, "We have a long, yellow box!" Thus, the binding mechanism pulls together a single representation of an object from several multimodal association cortices. Treisman et al.[16] and Julesz[17] have suggested that such associations require focused *attention*. They further divide the process into two steps. One is the *preattentive* stage in which the object is scanned for the size, shape, color, and movement by the parallel processing P and M pathways. A serial processing that is responsible for identifying how to categorize the visually constructed object follows. This categorization is dependent on the hippocampus and the eventual storage of the information about the object in the various association cortices.[9]

Attention is a function of working memory. Coward[18] proposed a model in which verbal working memory has two components: a subvocal rehearsal system of a phonological log accessed by reading words or numbers and a short-term memory store activated by speech. This "articulatory loop" allows us to retain phone numbers or addresses for short periods of time. He also demonstrated a nonverbal working memory that he called a *visuospatial scratchpad*. Both of these components are greatly dependent on the multimodal association areas of the frontal lobe and its executive function.

Until recently, we have assigned the basal ganglia to a simple role in motor behaviors. Recent work has demonstrated that they also play a key role in cognition, mood, and behavior.[20] Three circuits have been described that originate in the prefrontal association and limbic regions of the cortex and interact with specific areas of the basal ganglia. These areas of the frontal cortex are frequently the ones implicated in the deficits and behaviors seen in the TBI individual in the rehabilitation setting.

The first circuit is the *dorsolateral prefrontal* circuit (Figure 4.6), and this is the one frequently characterized by the term *director of executive functions*. It is the one most closely corresponding to the "articulatory loop" described by Coward[18] that is important for working memory. The circuit begins in the prefrontal cortex, projects to the basal ganglia, then to the thalamus, and back to the prefrontal cortex. This circuit undertakes cognitive tasks, such as organizing behavioral responses and using verbal responses in problem solving.

The second circuit is the *lateral orbitofrontal* circuit (Figure 4.7). This circuit begins in the lateral orbitofrontal

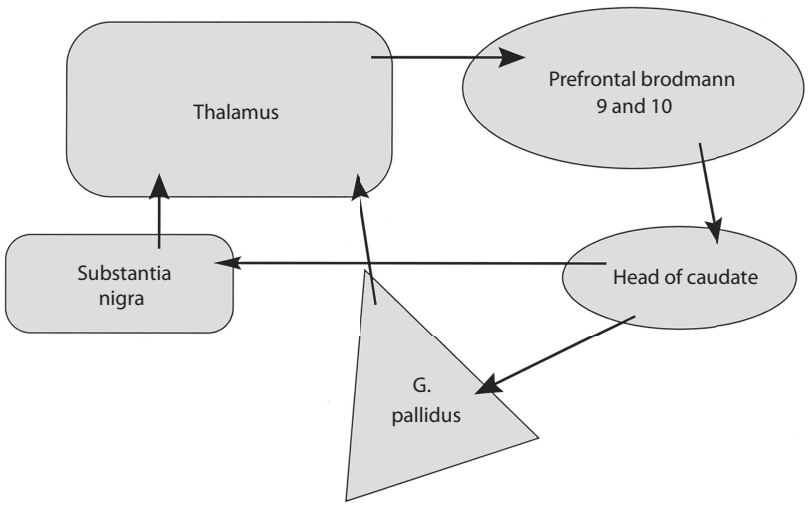

Figure 4.6 Dorsolateral prefrontal circuit.

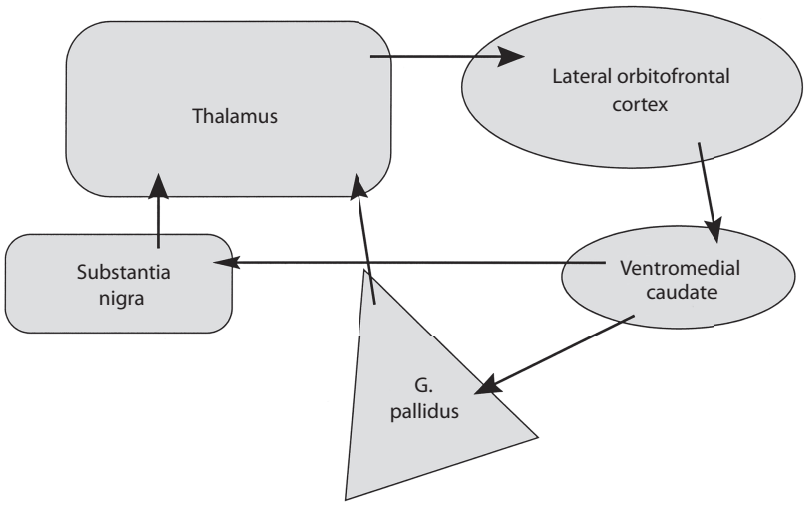

Figure 4.7 Lateral orbitofrontal circuit.

cortex, projects to the basal ganglia and to the thalamus, and returns to the orbitofrontal cortex. This circuit seems to be involved in mediating empathetic and socially appropriate responses. Injury to this area results in the individual being irritable and failing to respond to social cues.

The third circuit is the *anterior cingulate* (Figure 4.8). This circuit is distinguished by its role in motivated behavior, and it may play a role in conveying reinforcing stimuli to diffuse areas of cortical and subcortical regions.[19] This circuit begins in the anterior cingulate gyrus on the medial surface of the cerebral cortex and projects to the ventral striatum, which, in turn, receives inputs from the hippocampus, amygdala, and entorhinal cortices. From the ventral striatum, the projection goes to other parts of the basal ganglia, then to the thalamus, and back to the anterior cingulate gyrus. This particular circuit includes dopamine-containing neurons in the midbrain that have inputs to the basal ganglia. It has been suggested that these neurons may deliver reward-predictive signals. This circuit may be deeply involved in procedural learning, and, as such, this circuit may be important in the behavior modification programs in which reinforcement and reward are utilized.

MULTIMODAL REHABILITATION

Multimodal rehabilitation refers to a therapeutic approach that attempts to address the individual as a whole person. This places a responsibility on the rehabilitative team to address all of the rehabilitative possibilities. The process must address the physical aspects of movement and awareness of the environment as well as the cognitive, behavioral, social, and psychological aspects of the individual.

We have just discussed the role of the multimodal association cortices and their role in learning and memory.

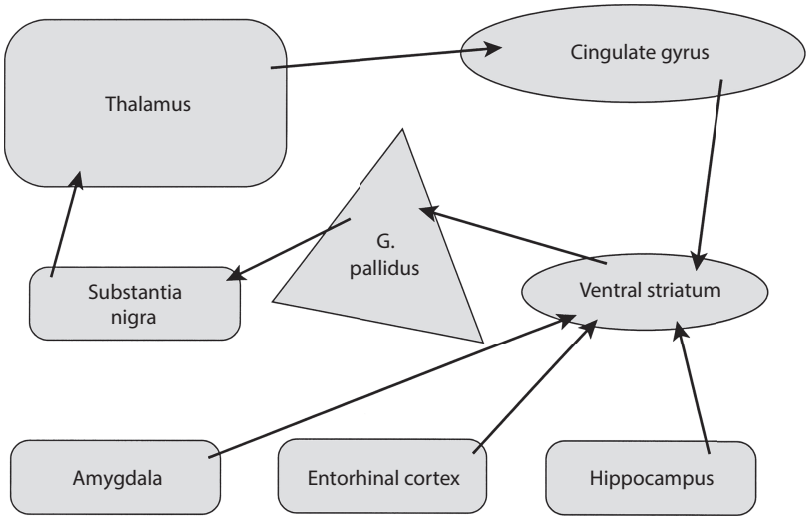

Figure 4.8 Anterior cingulate circuit.

It was shown that the long-term storage of memories was a function of the hippocampus distributing the component parts of the memory to the parietal, frontal, and temporal lobes. In a similar manner, we noted the distribution of the visual pathways to the multimodal, parietal, and temporal cortices. And the three circuits of the basal ganglia were related to the limbic and frontal association cortices. Wopert, Pearson, and Ghez provided an excellent overview of the association areas of the cerebral cortex and how these structures form the foundations for the cognitive capabilities of the brain.[20]

In each of these descriptions of the related pathway, we mentioned the route through the thalamus. The thalamus is a central structure of ancient origin. Before the development of the cerebral cortex, there was a thalamus that performed the functions of integrating the sensory and motor functions of the organism. It acts as a gatekeeper for information that is conveyed to the cerebral cortex.[21] In this role, it is central to the integration of all the sensory modalities except olfaction. In addition, it plays a role in the extrapyramidal motor output from the basal ganglia as well as the three mentioned basal ganglia–cortical circuits concerned with cognition, mood, and behavior.

The thalamus is composed of several nuclei that have different roles (Figure 4.9). Some of the nuclei function for specific sensory modalities, such as vision and auditory functions. Others have a motor integrative function, such as pathways to the extrapyramidal tract. Then, others are of a diffuse nature to serve the organism's arousal system. In any case, it is important for the therapist to remember that the thalamus holds the potential to be involved in many of the observed deficits of the head-injured person.

NEUROGENESIS IN ADULT HUMANS

The old concept that we are born with all the neurons we will ever have and that some neurons die off over our lifetime was recently found to be false. This long-held belief was overturned in an elegant experiment. P. S. Eriksson of Goteborg University, Sweden, and F. H. Gage of the Salk Institute, San Diego, California demonstrated that new neurons, as defined by biological markers, are generated from dividing progenitor cells in the dentate gyrus of adult humans.[23] Further, they indicated that the human hippocampus retains its ability to generate neurons throughout life. Exciting prospects and intensive investigations are

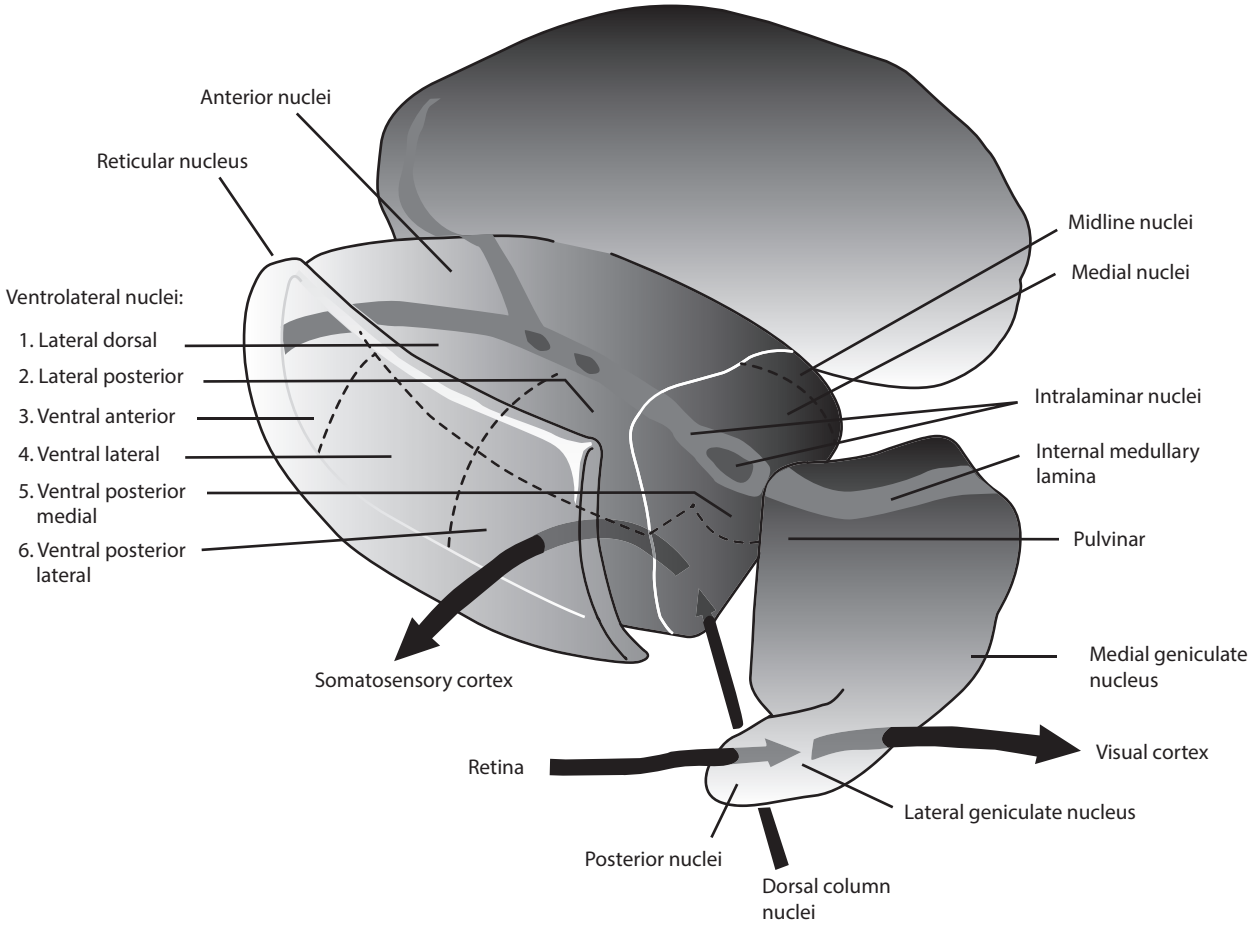

Figure 4.9 The major subdivisions of the thalamus. (From Amaral, D. G., The functional organization of perception and movement, in *Principles of Neural Science*, 4th ed., Kandel, E. R., Schwartz, J. H., and Jessell, T. M., Eds., McGraw-Hill, New York, 2000, p. 343. Used with permission.)

underway. Their work was built upon that of Elizabeth Gould who had demonstrated this phenomenon in macaque monkeys. She has subsequently shown that some of these new neurons have an apparent transient existence of only 9 weeks.[24]

This transient existence perhaps holds some promise for utilization for future therapies. Cramer et al.[2] have demonstrated that there are multipotent precursor cells able to generate neurons, astrocytes, and oligodendrocytes in the human brain. And, further, that these precursor cells are widely distributed, having been found in many brain regions studied, including the temporal and the frontal cortex, the amygdala, the hippocampus, and the periventricular zone. This work demonstrates a possible new platform to study adult human neurogenesis.

A summary of recent work that reflects on the restoration of function indicates that it requires synaptic regeneration even with precursor cells for regions of the injured brain. The injured environment is altered so that the previously permissive nurturing one is altered to make synaptogenesis difficult. In order for the synapses to be regenerated, the proper target must be found by the seeking axon. The postsynaptic membrane must be responsive to the particular neurotransmitter that is released. The proper supporting cells must be viable. The milieu of the surrounding environment must be one of balance of the proper ions and nutrients. Last, several key factors that limit regeneration of central axons have been identified, and the hope is that, through manipulation, regeneration of synapses may be enhanced.[21]

The discovery of the multipotent precursor cells and the work on manipulating the factors that limit regeneration of central axons suggest that the possibility of transplantation and the rehabilitation of the individual in an enriched environment hold promise for development and recovery of lost functions. The synaptogenesis stimulated by the activity-dependent therapeutic setting should give the cellular basis of learning we have been discussing a strong chance to bring about the rehabilitative results we want.

However, these prospects remain speculative but tantalizing and will require much further experimental effort to develop to their potential for rehabilitation.

CONSTRAINT-INDUCED THERAPY

More recent has been the discovery of *constraint-induced* (CI) therapy for stroke victims.[25] This therapy restricts the movements of the undamaged limb in order to make maximum use of the appendage that has been impaired. This therapy is not limited to limb movement, but has been seen to be useful in therapy for language disorders, such as aphasia.[26] Such restriction of movement to the impaired structure causes changes in the brain, altering the synapses, and enhancing the neuronal connections. These changes can take several forms, such as the assumption of the function by the same region in the other hemisphere, a change in the type of sensory processing from one modality to a new one, or an enlargement of a functional brain region due to its expanded use.[27]

In a like manner, it has been demonstrated that exercise, and not just motor activity, can produce physical changes in the brain structure.[28] Gómez-Pinilla has demonstrated in experimental animals that an increase in challenging exercise activity potentiates the effects of physical activity on trophic factor induction in the cerebellum and that the trophic factor involvement in behavior may provide a molecular basis for the enhanced cognitive function associated with active lifestyles and may guide development of strategies to improve rehabilitation. In addition to the experimental animals, changes that take place in the human motor cortex have been demonstrated with neuroimaging.[29]

This change wrought by the action of the therapist on the impaired person brings about the positive result of rehabilitation. It is the active interaction of the therapist, client, and the environment that causes physical changes in the structure of the brain that have formed the basis of all the therapies ever used. It is only in the last decade or so that we have been able to demonstrate that these changes are taking place at the level of the neurons. These changes in the brain tissue have been demonstrated conclusively by the new neuroimaging technology.[30]

SUMMARY

These are exciting times for researchers and rehabilitation specialists alike. The prospect of new possibilities is incentive to press the frontiers of knowledge. However, it should be remembered that therapies have worked for years without a clear understanding of the underlying foundations of the changes wrought on the brain itself. The constant repetition of the target activity has brought about restoration of function. It is with the deeper knowledge of the changes in the brain that do occur that insights into new therapies may develop.

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5

Environmental enrichment: A preclinical model of neurorehabilitation for traumatic brain injury

CORINA O. BONDI AND ANTHONY E. KLINE

TRAUMATIC BRAIN INJURY IS A SIGNIFICANT HEALTH CARE ISSUE

Traumatic brain injury (TBI) ranges from minimal concussions to severe anatomical abnormalities and pathophysiology.[1–3] More than 10 million people worldwide incur a TBI yearly and approximately 2 million reside in the United States.[4] In the United States alone, there are more than 500,000 emergency room visits for TBI and 50,000 deaths.[5–9] Furthermore, more than 100,000 TBI patients sustain motor and cognitive dysfunction that can persist for years, if not indefinitely. Moreover, the economic burden resulting from acute hospital care to long-term rehabilitation, as well as lost productivity, is enormous with estimates in the billions of dollars each year.[7–10] Last, although the emotional toll of TBI on an afflicted individual's interpersonal relationships is immeasurable, the associated strains are certainly impactful and play a significant role in the recovery process. Indisputably, TBI is a significant health care issue that warrants discovery and subsequent refinement of therapeutic strategies. Success in this avenue will promote a level of enhanced function that will afford TBI patients the ability to engage in healthy relationships as well as regain their role in society as contributing members.

Numerous treatment approaches, such as pharmacotherapies, hypothermia, and the endogenous administration of neurotrophic factors, have been evaluated over the past several years and have demonstrated significant benefits in the laboratory,[1,11–16] but few, if any, have successfully translated to the clinic.[17,18] The absence of clinical efficacy by these traditional treatment strategies as well as the robustness of environmental enrichment (EE) to enhance behavioral outcomes and produce neural changes in noninjured rats[1,19] provided the impetus for evaluating alternative approaches for the treatment of TBI. Approaches such as exercise, low-level laser therapy, constraint-induced movement therapy, and EE have been shown to benefit outcome after TBI.[20] However, EE has emerged as the most effective and consistent paradigm with benefits reported after TBI produced by several models (for excellent reviews see[1,16,19,20]) and with varying initiation time frames.[1,19–23] Hence, the aim of this chapter is to discuss the studies utilizing EE after TBI that have demonstrated improvements after TBI as well as describe potential mechanisms for EE-induced benefits. As will be elucidated, these findings lend support for EE as a preclinical model of neurorehabilitation.

EE DEFINED

EE is an experimental housing situation in which rodents are exposed to multiple objects of various shapes and sizes in an expansive living space. Another salient feature of EE is the housing of several rats together, which affords the opportunity for integration of exploratory, physical, and social elements. This milieu is strikingly different from standard (STD) housing in which single or paired rats live in traditional laboratory-sized cages with only food and water. EE has been shown to exert numerous plasticity-associated

alterations,[24–26] which are often accompanied by significant behavioral improvements in normal (i.e., noninjured) rodents as well as in several models of central nervous system (CNS) syndromes.[27–31] As described in the subsequent sections, EE also promotes cognitive and motor improvement and attenuates histopathology after TBI in rodents.[1,16,19,20]

EE AS A POTENTIAL THERAPEUTIC APPROACH: EARLY SUPPORT

The protective and reparative effects of EE after brain injury have been known since the 1970s when Will and colleagues reported improved performance on a Hebb-Williams task following occipital cortex injury in neonatal and young adult rats.[32,33] The reemergence of studies in the mid-1980s demonstrating marked motor protection when provided prior to or after bilateral sensorimotor cortex lesions[34–36] further promoted the interest in EE as a potential therapeutic approach after brain trauma.

EE AS A POTENTIAL THERAPEUTIC APPROACH: FURTHER SUPPORT

In addition to the lesion studies described in the preceding section supporting EE as a potential therapy after brain injury, several studies incorporating more clinically relevant models of brain trauma, such as the well-validated and most used controlled cortical impact (CCI)[37] and fluid percussion (FP),[38] have also been utilized to evaluate the effects of EE. Both models produce long-lasting cognitive and histological deficits[39–43] and, thus, mimic the clinic. With the advent of blast brain injury, the potential efficacy of EE in this model is also being evaluated and is discussed briefly, as is a study using the weight drop method.

The first TBI study describing the effect of EE used an FP brain injury model and was conducted by Hamm and colleagues, who produced an injury of moderate severity.[44] Following TBI or sham injury, the rats were placed in a complex environment (i.e., EE) or STD housing, and spatial learning was assessed in a Morris water maze (MWM).[45] Rats receiving the EE performed markedly better than the non-EE rats. Moreover, demonstrating the robust efficacy of EE, the TBI rats in the complex environment did not differ statistically from the sham controls.[44] Passineau and colleagues also used the FP injury model but produced a more severe injury and showed that EE rats learned the location of the escape platform in the MWM significantly faster than the STD-housed group. EE was also reported to attenuate cortical lesion volume when quantified 2 weeks after the TBI.[46] Cognitive improvements, as well as motor enhancement and histological protection, have been reported in other laboratories producing TBI via the FP model in adult[47–55] and pediatric[56–58] rats. EE has also been shown to confer locomotor improvement and reduce striatal cell loss in adult mice subjected to an FP injury.[59] This finding extends the benefits of EE to various animal models and, thus, strengthens its applicability as a therapeutic strategy.

Similar benefits have been reported by EE after CCI injury. Smith and colleagues demonstrated that rats recovered forelimb function significantly faster than non-EE rats following a CCI injury to the forelimb region of the rat sensorimotor cortex.[60] Briones and colleagues showed that EE provided continuously for 4 weeks recovered TBI-induced deficits in swim latency and nonmatching-to-sample task errors.[61] As previously stated, the typical EE paradigm consists of three basic components, which include increased space for exploration and exercise, sensory experience, and socialization. To determine what component was most critical for the EE-mediated benefits, Sozda and colleagues designed a study to address this important point.[62] After a CCI injury of moderate severity, the rats were placed in various EE conditions that remained complete or had one or more components removed and, hence, were referred to as typical or atypical, respectively. The typical EE had all the components present, and the atypical had the large space, toys, or social components removed. The data showed that the typical EE paradigm produced the greatest benefit in motor, cognitive, and histological outcome relative to the atypical EE groups. Importantly, the atypical EE groups also exerted slightly better outcomes than the STD housed rats. The data suggest that all components of the EE paradigm are necessary to provide an optimal EE effect.[62] This finding may have clinical implications for rehabilitation in that it endorses multimodal rehabilitation for TBI patients versus simple motor or cognitive training.

EE has also been reported to exert benefits after blast TBI (bTBI) produced via a compression-driven shock tube as reported by Kovesdi et al.[63] Following the bTBI, the rats were evaluated for behavioral performance on the elevated plus maze (EPM) and Barnes maze commencing on day 15 and extending to day 66 postinjury. EE did not normalize anxiety postinjury on the EPM. However, EE did significantly improve spatial memory performance in the Barnes maze compared to the non-EE rats.[63] Furthermore, the signaling protein vascular endothelial growth factor, a positive regulator of adult hippocampal neurogenesis,[64] and tau protein, a marker of axonal degeneration, were normalized in the dorsal hippocampus in the rats exposed to EE. EE also reduced IL-6 expression in the ventral hippocampus.[63] That EE is able to provide benefit in a model of bTBI, which is taking on more significance given the nature of injuries in the military, strengthens the paradigm.

The effects of EE have also been evaluated after TBI using a weight drop mode.[65] Following injury, mice were immediately placed in EE for 6 weeks. Cognitive performance was assessed using the novel object recognition and EPM tasks. The data showed that the TBI mice housed in STD conditions were significantly impaired in both tasks relative to the enriched TBI mice. Moreover, no differences were revealed between the control and the injured EE mice.[65] The benefits of EE, in yet another model of TBI, lend further support for EE as a generalized rehabilitative strategy after brain trauma.

BENEFITS OF EE ARE NOT GENDER DEPENDENT

The consistent benefits of EE described thus far, regardless of whether in adult or pediatric rats or adult mice, have all occurred in males. Given the fact that females account for a large percentage of the clinical TBI population, it is critical to determine the potential efficacy of this approach not only because they are also in need of rehabilitation, but to further bolster EE as a therapeutic paradigm with clinical relevance. Moreover, females are grossly understudied in experimental models of TBI and even more so in preclinical rehabilitation paradigms. In an attempt to address this oversight, adult normal cycling female rats received a CCI injury of moderate severity followed by immediate initiation of EE that continued throughout the duration of the experiment.[66] The findings revealed that EE improved motor performance on a number of motor-associated tasks, such as beam balance, beam walk, and rotarod relative to STD-housed controls. EE also hastened spatial learning in a MWM task and provided significant histological protection.[66] This study was the first to demonstrate that EE benefits female rats on a variety of end points post-TBI, which replicates the studies in males. That EE can provide functional benefits and histological protection provides further support for EE as a preclinical model of neurorehabilitation. Several unpublished studies in our laboratory continue to show that EE consistently rehabilitates females.

BENEFITS OF EE ARE ENDURING

To this point, the studies described have not evaluated the long-term efficacy of the EE-mediated benefits as the subjects were sacrificed after the initial reported findings. However, demonstrating longevity is critical for any effective therapy, and, thus, showing that the benefits induced by EE endure despite its discontinuance would strengthen the validity of EE as a preclinical model of neurorehabilitation. Hence, to determine whether the benefits can be maintained after EE (i.e., rehabilitation) is discontinued, Cheng and colleagues subjected rats to a CCI or sham injury and managed them during two phases.[67] During phase 1 of the experiment, the rats were randomly assigned to 3 weeks of EE or STD housing. Assessment of motor and cognitive performance was conducted while the rats were in their respective environments. The findings showed that behavior was significantly improved in the EE group relative to STD controls, which replicated previous studies. In phase 2 of the experiment, half of the rats that recovered in the EE condition were transferred back to STD conditions, which mimicked the withdrawal of rehabilitation. In this phase, the groups were retested for motor and cognition at 1-month intervals for 6 months. Demonstrating long-term efficacy, the EE-continuous and EE-withdrawal groups performed at the same level and were both significantly better than the STD-housed group.[67] These data indicate that EE-induced motor and cognitive benefits are maintained for up to 6 months following the cessation of EE.

THERAPEUTIC WINDOW OF EE IS FLEXIBLE

Because TBI patients will not engage in rehabilitation until after critical care has been completed, it is important to demonstrate that a preclinical model of neurorehabilitation can be effective even when initiated beyond the time point used in the typical EE studies presented up to this point. To begin addressing the therapeutic window of EE, Hoffman and colleagues designed an experiment that could answer this important question.[21] After a CCI injury of moderate severity, the rats were divided into groups that received EE or STD housing immediately after surgery and remained in that condition until the end of the experiment or EE for only 1 week after surgery or, alternatively, EE for only the last 2 weeks of the experiment (with STD housing the first week). The data showed that rats provided early (immediately after surgery) and continuous EE postinjury recovered from the motor deficits and acquired spatial learning significantly quicker than STD-housed rats, which replicated previous studies using the typical EE paradigm. The data further showed that delaying EE by a week after TBI still enhanced cognition, but did not benefit motor function. Exposing the rats to EE immediately after TBI, but only for a week, facilitated the recovery of the motor deficits but did not benefit spatial learning. The findings suggest that EE-induced benefits are contingent on task-specific neurobehavioral experience.

To further characterize the EE timing issue, Matter and colleagues expanded on the study by Hoffman and colleagues[21] by incorporating additional temporal permutations.[23] Using the same injury parameters as described in the previous study,[21] rats were randomly assigned to eight groups receiving continuous, early, delayed, or intermittent EE. As in the initial study assessing temporal manipulations, early EE enhanced motor recovery, and late EE facilitated cognitive recovery. The TBI group that received EE for a total of 14 days (1 week prior to and during maze training) performed significantly better than both the TBI groups receiving different timing permutations.[23] This latter finding suggests that there may be a required threshold of two contiguous weeks of EE in order to effectively promote cognitive benefits after TBI.

Another important variable to consider when refining the EE model is that the duration of clinical rehabilitation is significantly limited. Studies indicate that in the clinical setting, therapy is typically provided for periods of 3–8 hours,[68–71] which is markedly less than the continuous EE provided to the rats in the studies described up to this point. In an effort to refine the experimental model so that it conforms closer to the clinic, de Witt et al. evaluated the potential efficacy of an abbreviated enrichment (i.e., rehabilitation-relevant) paradigm that consisted of 2,

4, or 6 hours of EE per day and compared these groups to those receiving either continuous EE or STD housing.[22] The data revealed that 6 hours of EE per day was sufficient to induce improvements in motor and cognitive performance. The 6-hour EE group performed significantly better than the groups receiving 2 or 4 hours of EE or STD housing. Importantly, the 6-hour EE groups did not differ from the continuous EE group, indicating that abbreviated EE is sufficient for promoting optimal functional benefits after moderate TBI in rats. However, no statistical differences were revealed between the 2- or 4-hour EE groups versus the STD group, suggesting that there is a minimum threshold of daily EE exposure required to enhance performance after TBI. The 6-hour rehabilitation paradigm is consistent with the timing provided to clinical TBI patients.[68–71]

Although a few studies have reported EE-induced benefits with lesser exposure, the methodological procedures, such as brain injury, behavioral tasks, and assessment protocols for those studies were significantly different from the ones conducted by Kline and colleagues.[21,22,62,66,67] Specifically, 1 hour of EE per day was reported to be sufficient to enhance cognitive recovery after FP injury.[72] TBI-related impairments of spontaneous object recognition in a Y-maze were reversed when EE exposure was provided for only 2 hours per day.[73] Taken together, these studies suggest that EE can provide benefits after CNS injury, but like other therapies, there may be a limit to its efficacy that is dependent on timing, dosing, and injury.

EE: COMBINATION THERAPY PARADIGMS

Due to the limited success of positive monotherapy preclinical findings extending to the clinic, a recent approach is to investigate the use of combined or polytherapies.[74,75] In this vein, one approach that has received attention is pairing EE with the serotonin$_{1A}$ (5-HT$_{1A}$) receptor agonist 8-hydroxy-2-(di-*n*-propylamino) tetralin (8-OH-DPAT), which has been shown to promote behavioral recovery and restore neuropathological alterations post-TBI.[76–78] In the first of a series of combination experiments, Kline and colleagues sought to investigate whether combining 8-OH-DPAT acutely with continuous EE would confer additional benefit relative to either treatment alone.[79] Rats received a CCI injury of moderate severity and 15 minutes later were provided a single administration of 8-OH-DPAT and subsequently exposed to early and continuous EE. The results demonstrated that both 8-OH-DPAT and EE enhanced behavioral recovery and attenuated hippocampal CA$_3$ cell loss as seen in previous studies.[76–78] Specifically, both EE and 8-OH-DPAT significantly reduced the time to traverse an elevated narrow beam and to locate the escape platform in the MWM task in both groups versus the STD-housed vehicle group. The combination of EE and 8-OH-DPAT also enhanced spatial learning versus the STD plus 8-OH-DPAT group, which suggested that EE enhanced the effect of 8-OH-DPAT. A caveat to this interpretation is that there were no significant differences in behavioral recovery between the combination treatment group and the EE-alone group, which indicates that there was no additional benefit when overlapping the two therapeutic strategies.[79]

Studies from Kline and colleagues have also shown that chronic 8-OH-DPAT reduces histopathology (i.e., decreases cortical lesion volume and enhances hippocampal neuron survival) and improves neurobehavioral recovery after CCI injury.[80] Given the lack of an additive effect with the single administration paradigm, a subsequent study was designed to more closely mimic the clinical setting in which TBI patients would receive neurorehabilitation and would also be given pharmacotherapies chronically. To this end, EE was provided along with daily administrations of 8-OH-DPAT for 3 weeks postinjury.[74] The data revealed cognitive and motor recovery as well as reduced hippocampal CA$_3$ and choline acetyltransferase (ChAT) medial septal cell loss with each therapy. No added behavioral effect was observed with the combination treatment, but there was a significant reduction in TBI-induced ChAT cell loss.[74] The authors have suggested that a lack of an additive behavioral effect in some of the reported measures may stem from the fact that the typical EE paradigm (i.e., early and continuous) confers robust effects on its own, and, thus, there may be a ceiling effect that precludes 8-OH-DPAT from providing additional statistically significant improvement.

Buspirone is also a 5-HT$_{1A}$ receptor agonist that has been previously shown to facilitate cognitive performance in a MWM task and reduce histopathology after TBI.[81] Importantly, it is used in the clinical setting to treat anxiety and depression and, therefore, safety and tolerability parameters are well characterized.[82] To enhance the clinical translation of single-therapy studies, Kline and colleagues placed CCI-injured or sham adult male rats into EE or STD housing and subsequently administered either chronic buspirone or vehicle.[83] TBI animals in EE, regardless of whether buspirone or vehicle-treated, displayed diminished CA$_3$ hippocampal cell loss as well as enhanced motor and cognitive function compared to STD housing. Buspirone alone also facilitated neurobehavioral recovery in the TBI rats. As seen with the previous combination studies reported thus far, there was no additive effect when buspirone and EE were combined.[83] In marked contrast, the same therapeutic approach of EE and buspirone in CCI-injured pediatric rats led to improved performance relative to the buspirone and EE treatments alone as a significant enhancement of spatial learning, and reduction of lesion size was observed versus the STD controls.[84] Although several differences exist between adult and pediatric rats, one plausible explanation for the additive effects observed in the pediatric rats versus the adults may be an enhanced sensitivity to EE resulting from a burst of synaptogenesis and subsequent changes in synaptic efficiency associated with memory processing.[85]

Alternative combination therapeutic approaches utilizing stem cells as an adjunct to EE were recently reported. Peruzzaro et al. investigated the potential effectiveness of EE plus murine cortical embryonic stem cell (eSCs). Rats were subjected to a bilateral prefrontal CCI injury and then

placed in EE for 5 weeks.[86] The data showed that the combination of eSC implants plus EE exposure was not convincingly effective at facilitating recovery in the rotarod and Barnes maze tests as the combination treatment group performed similarly to controls. The direct functional relevance of eSC implantation combined with EE remains to be determined as stringent quantitative analyses for eSC survival, migration, and differentiation into neural or glial cells were not performed.[86] Follow-up studies from the same group of investigators provided induced pluripotent stem cells bilaterally around the contusion site following CCI injury to the medial prefrontal cortex (MPC). The data showed that the combination treatment group performed better in the water maze task.[87] In a more recent study, Nudi and colleagues tested the effects of three separate therapies (EE, progesterone, and embryonic neural stem cells [eNSCs]) on well-established motor and cognitive tasks after a CCI in the MPC.[88] The authors reported improved functional outcomes on several of the behavioral tasks in animals receiving combinational therapies that included EE. Moreover, the immunohistochemical findings showed that the transplanted eNSCs survived, migrated, and displayed neural phenotypes.[88]

POTENTIAL MECHANISMS MEDIATING EE-INDUCED BENEFITS

Numerous studies have reported significant changes in neurotrophin expression after TBI.[47,89–93] Hicks et al. reported increased expression of brain-derived neurotrophic factor (BDNF) mRNA in the CA_3 and dentate gyrus at 1, 3, and 6 hours after FP injury.[89] Moreover, BDNF in the dentate gyrus remained significantly elevated for up to 72 hours. In the same study, NT-3 mRNA was significantly reduced at 6 and 24 hours postinjury. Together, these findings suggest that secondary events after TBI are multifaceted and include plasticity. Because EE has been shown to modulate neurotrophins in non-TBI animals,[94–96] Hicks and colleagues sought to evaluate the role of EE in neurotrophin expression after TBI.[47] The authors report that 2 weeks of EE improved acquisition of spatial learning in FP injured rats, but did not alter BDNF, trkB, and NT-3 mRNA levels in hippocampal subregions.[47]

Significant alterations in dopamine (DA) levels and transmission have been reported in rodents following EE[14,97] or CCI injury.[98–100] Hence, Wagner and colleagues sought to investigate gender-dependent responsiveness to EE and DA regulation after TBI. Male and normal cycling female rats were subjected to CCI and then placed into EE or STD housing conditions for 4 weeks. Dopamine transporter (DAT) protein expression was subsequently quantified in the frontal cortex and striatum.[101] The findings indicated that DAT expression in males underwent larger decreases after CCI relative to females, but EE has bigger effects on postinjury DAT expression in females.[101] Shin et al. characterized the mRNA expression profile in the substantia nigra and ventral tegmental area at 4 weeks postinjury in STD- and EE-housed rats to assess differential gene expression.[102] Alterations in genes involved in inflammation and cellular plasticity, as well as chronic alterations in genes important for calcium and DA signaling pathways, were observed in TBI animals exposed to EE (i.e., downregulation of tyrosine hydroxylase and upregulation of α-synuclein). These changes may represent compensatory mechanisms to counteract the detrimental effects of TBI.[102]

Additional mechanisms mediating the benefits conferred by EE have been put forth by Briones and colleagues[61] who reported that EE reversed the injury-induced increases of the proinflammatory cytokines IL-1β and TNF-α. EE also attenuated the TBI-induced decrease of the anti-inflammatory cytokine IL-10 in the prefrontal cortex and hippocampus. Moreover, continuous EE normalized the ratio of phosphorylated adenosine monophosphate-activated protein kinase (pAMPK)/AMPK and the ubiquitous mitochondrial creatine kinase (uMtCK), which are markers of brain energy homeostasis.

These mechanistic studies demonstrate region-specific and gender differences in potential molecular underpinnings mediating EE-induced recovery. Although complex, the elucidation of such diverse alterations may provide new avenues for pharmaceutical targets and rehabilitative approaches after TBI.

CAVEATS TO THE EE EFFECT

To this point, the overwhelming consensus has been that EE consistently confers benefits after TBI. However, there are reported instances when EE did not support the hypotheses. Examples include greater initial forelimb deficits and larger contusion cavities in rats enriched for 15 days during postweaning[103] and a lack of behavioral improvement in FP-injured rats placed in EE for 45 minutes per day beginning 1 week after injury.[104] Some of these limitations may have been due to differential timing parameters as reported earlier. EE also did not ameliorate anxiety or depression-like symptoms in rats after a CCI injury to the medial frontal cortex.[105]

CONCLUSION

Although there are a few cases in which EE as a therapy after TBI did not support the stated hypotheses, those instances are in the minority as the overall conclusion from the studies described is that enrichment confers significant functional and histological outcome in male and female rodents regardless of age and model of injury used. These cumulative findings support EE as a generalized and robust preclinical model of neurorehabilitation. However, to further refine the model so that it more accurately mimics the clinic, additional experimental paradigms should be considered. For example, manipulating the timing of initiation and duration of EE exposure would lead to a model that more closely mimics real-world applications of neurorehabilitation. Further studies combining other therapeutic

approaches in search of additive or synergistic effects would further strengthen the model. Indeed, the combination of EE and buspirone after pediatric CCI injury produced additive effects on recovery. Although some potential mechanisms for the EE-induced benefits were described, additional studies are needed.

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6

Neuroanatomy of basic cognitive function

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INTRODUCTION

Traumatic brain injury (TBI) involves an unpredictable and wide array of neurological structures. The clinician is faced with a tremendous variety of clinical presentations as a result. Advances in neuroscience have been considerable in the last two decades, and knowledge of neurological anatomy and physiology has improved tremendously. Knowledge of the basic anatomy and physiology of the brain is important for understanding behavioral manifestations following injury at a minimum. That same knowledge should be integral to theoretical constructs and rationales for the development of treatment approaches for cognitive dysfunction following TBI.

The most basic levels of cognition relate to how information enters the central nervous system (CNS) and is gathered, moved, reduced, used, and stored. To understand the role of structures and regions in the brain in cognitive and other function has been a long-standing desire. From the earliest attempts at phrenology to the latest technologies, the task remains intriguing and alluringly elusive. This chapter provides a neuroanatomical foundation for understanding the flow of information in the brain. That said, the best this chapter can do is approximate an understanding of the structural organization of the brain and its structural connectivity. Although this is certainly important, more recent expeditions into functional connectivity have provided additional information about network or regional functional specificity and provide a means for distinguishing or classifying subjects based upon specified measures of distributed brain activity. A third approach, effective connectivity, strives to enable generative models to test hypotheses of how the brain works. In the combination of structural, functional, and effective connectivity, insight can be furthered as to the nature of how the brain works.[1] The discussion can go beyond the pages that follow although, to be sure, the complexity of the brain will require tremendous advances in our investigations and technologies to do so. This chapter provides a review of the anatomy that underlies information processing and a review of some aspects of the physiology of learning and memory.

Sensory systems

Information flow throughout the CNS is a primary concern for cognitive function. Tactile sensory pathways include those responsible for pain and temperature (lateral spinothalamic tract), those responsible for conscious proprioception and discriminative touch (dorsal column–medial lemniscal pathway), and those responsible for unconscious proprioception (ventral and dorsal spinocerebellar tracts) (Figure 6.1). The lateral spinothalamic tract synapses in the

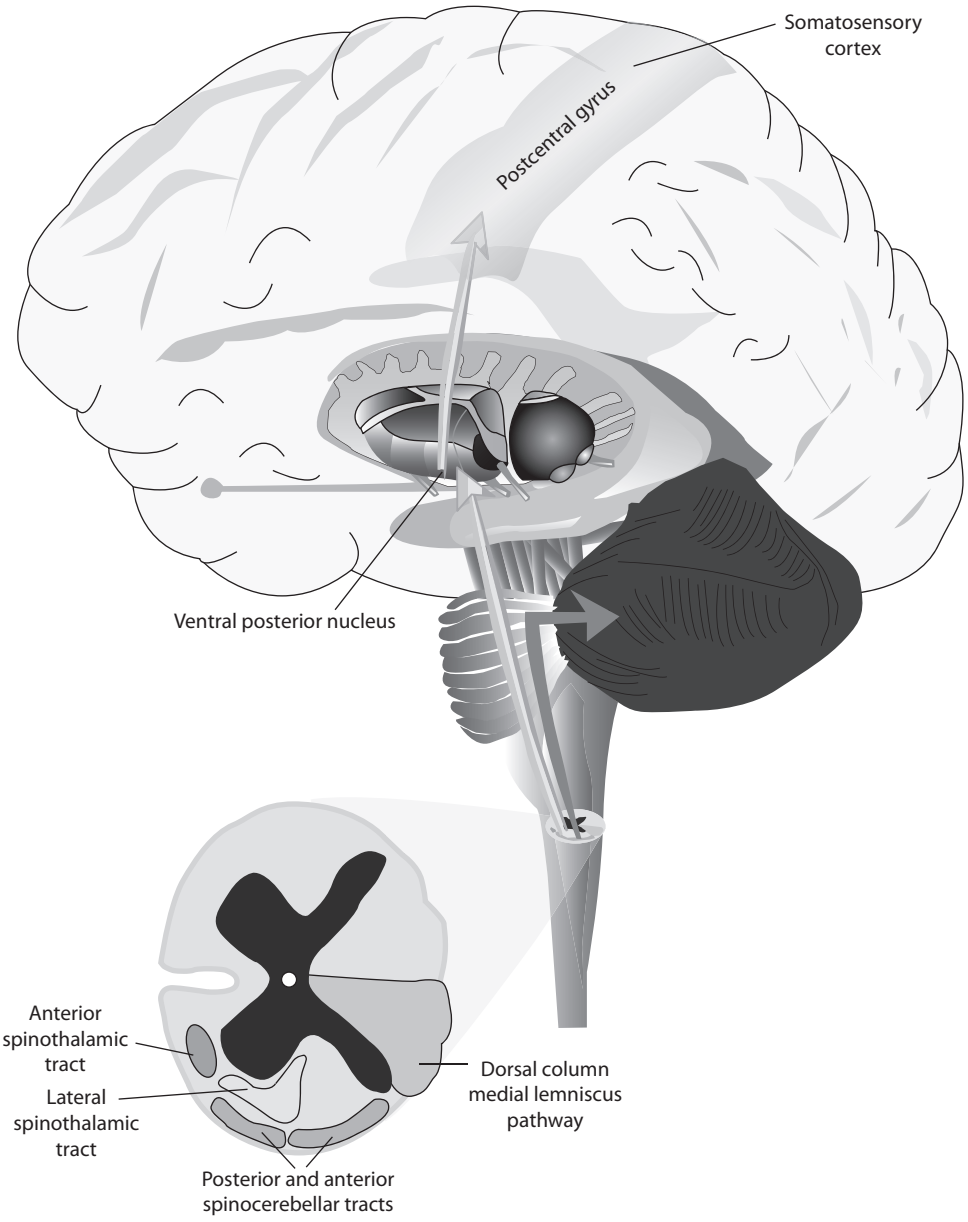


Figure 6.1 **(See color insert.)** Diagram of spinothalamic tract at the level of the spinal cord, brain stem, thalamus, and parietal cortex. Colors correspond to specific portions of the pathway.

ventral posterior thalamic nucleus and projects via thalamocortical fibers of the posterior limb of the internal capsule to the sensory cortex in the postcentral gyrus of the frontal lobe. Collateral projections from the spinothalamic tract synapse in the brain stem within the reticular formation. The dorsal column–medial lemniscal pathway follows the same course as the lateral spinothalamic tract via the ventral posterior nucleus of the thalamus and posterior limb of the internal capsule on its way to the postcentral gyrus. The anterior spinothalamic tract, which is responsible for perceptions of simple touch, comprises a portion of the dorsal column. The ventral and dorsal spinocerebellar tracts terminate at the level of the cerebellum.

Visual stimuli enter the system at a supratentorial level, coursing from the retina via the optic nerve to the lateral geniculate nucleus of the thalamus (Figure 6.2). The stimulus progresses from the lateral geniculate nuclei via Meyer's loop and the geniculocalcarine tract before terminating in the calcarine fissure and lingual gyrus of the occipital lobe, respectively. Visual stimuli travel to the occipital primary sensory regions via both temporal (Meyer's loop) and parietal lobe (geniculocalcarine tract) structures, depending upon the quadrant of the visual field represented.

Auditory stimuli are first registered at the dorsal and ventral cochlear nuclei located in the pons (Figure 6.3). Auditory stimuli travel from these nuclei to the medial geniculate bodies of the thalamus before continuing to the auditory cortex of the temporal lobes. Vestibular stimuli also course through cranial nerve VIII, which synapses in the brain stem on the superior, medial, lateral, and inferior vestibular nuclei

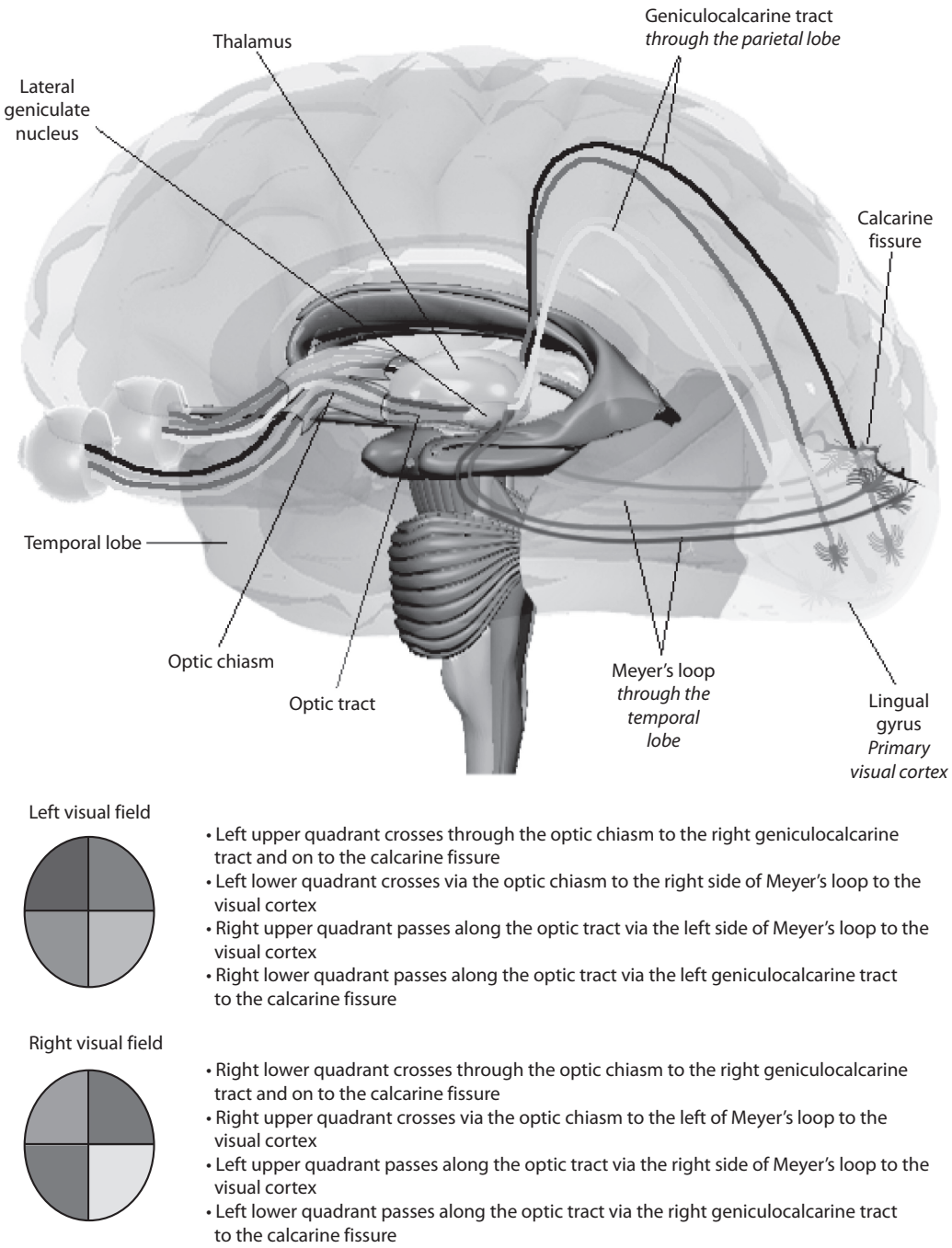


Figure 6.2 **(See color insert.)** Visual pathways from retinas, thalamus, geniculocalcarine tract, Meyer's loop, and occipital cortex.

located in the upper medulla and lower pons (Figure 6.3). Stimuli project from these nuclei to the spinal cord, cerebellum, reticular formation, and to the nuclei of the oculomotor (III), trochlear (IV), and abducens (VI) cranial nerves via the medial longitudinal fasciculus. Vestibular signals terminate in the primary sensory area of the parietal lobe, and auditory signals terminate in the superior temporal gyrus.

Olfactory stimuli travel from the olfactory bulb to the rhinencephalon and project to the piriform area of the medial temporal lobe, the anterior perforated substance and the terminal gyri of the medial basal frontal lobe, and the anterior uncus located in the medial surface of the temporal lobe (Figures 6.4 and 6.5). Olfactory stimuli also project to the amygdala and hippocampal gyrus. Like visual stimuli, olfactory stimuli enter the CNS at a supratentorial level. Olfactory stimuli reach the thalamus via projections from the piriform cortex and the amygdala. Odorant stimuli can reach the neocortex directly or indirectly via the thalamus.[2] The influence of olfactory stimuli on emotive state is supported by projections to the amygdala and hypothalamus. Pheromones signal via these same pathways. The orbitofrontal and frontal cortices are involved in conscious odor discrimination.

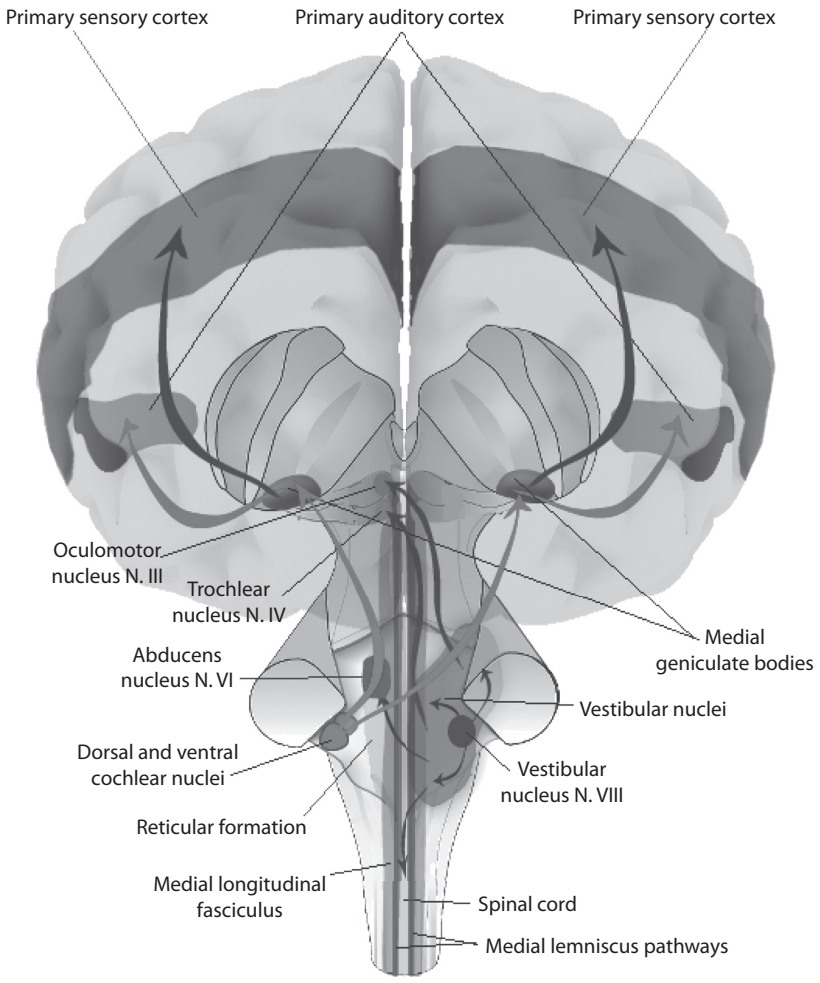


Figure 6.3 **(See color insert.)** Auditory and vestibular sensory pathways depicting brain stem nuclei, thalamic relays via the medial geniculate bodies, progressing to parietal and temporal cortices.

RETICULAR FORMATION

The pathways reviewed thus far are systems that relay to specific thalamic nuclei and act more directly upon the primary sensory cortices via various thalamic nuclei. The reticular formation acts indirectly to provide sensory input to the cortex, however, via the nonspecific thalamic nuclei (Figure 6.6). Projections from the nonspecific thalamic nuclei connect to all areas of the cortex. Afferent input to the reticular formation is provided from collateral branches of the spinothalamic and lemniscal pathways and information descending from the cortex through the corticoreticular pathways. The corticoreticular fibers include collateral branches of the corticospinal and corticobulbar tracts deriving from cortical areas that are widespread. The cerebellum, basal ganglia, hypothalamus, cranial nerve nuclei, and colliculi also provide afferent input to the reticular formation. The superior colliculus is implicated in the covert orientation of attention to visual space,[3] and the midbrain has been implicated in the orientation of attention and maintenance of arousal level.[4,5]

Reticular efferents deliver information from the reticular formation to the hypothalamus, the nonspecific nuclei of the thalamus,[6] and the descending reticulospinal pathway.[7] Pathways projecting from the reticular formation are part of the ascending projectional system.

Hypothalamus, pituitary, thalamus, and basal ganglia

HYPOTHALAMUS AND PITUITARY

A primary function of the hypothalamus is regulation of the autonomic nervous system. The hypothalamus integrates autonomic response and endocrine function with behavior to maintain homeostasis of certain systems. Blood pressure and electrolyte composition are maintained by control of drinking and salt appetite. Body temperature is regulated by control of metabolic thermogenesis and behaviors that seek to warm or cool the individual. Energy metabolism is regulated by feeding, digestion, and metabolic rate. Reproduction is regulated through hormonal control. Finally, emergency responses to stress are controlled by regulating blood flow

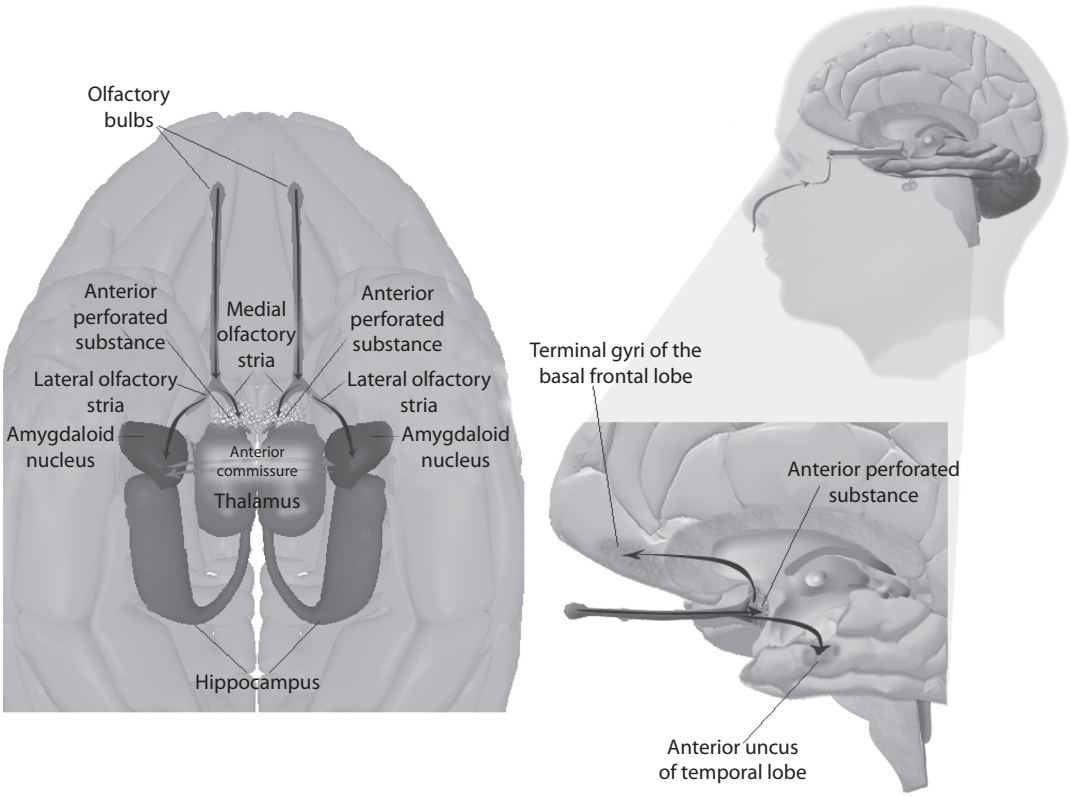


Figure 6.4 **(See color insert.)** Olfactory system: Olfactory bulb to anterior perforated substance to anterior and frontal lobe. Inferior and medial views.

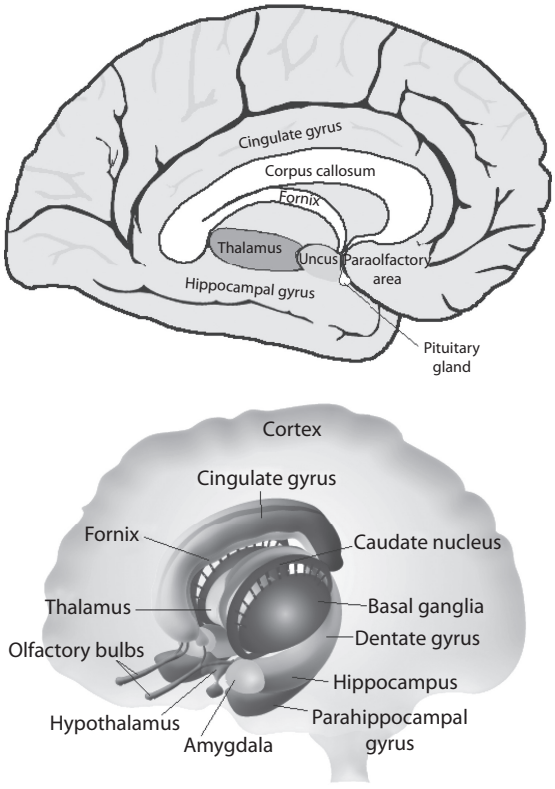


Figure 6.5 **(See color insert.)** Medial and 3-D views of olfactory bulb, amygdala, thalamus, uncus, and paraolfactory area.

to muscle and other tissues and release of adrenal stress hormones. The hypothalamus receives inputs of sensory information from all over the body; compares this information to biological set points; and, upon detection of deviation from the set points, adjusts autonomic, endocrine, and behavioral responses to return to homeostasis.[8]

Hypothalamic influence is exerted directly upon the pituitary. The pituitary controls hormone production by serving as a feedback mechanism rather than by direct production of hormones. The anterior pituitary regulates the sex hormones, prolactin, growth hormone, and cortisol. The posterior pituitary regulates antidiuretic hormone and insulin production (Figure 6.7). The anterior pituitary or adenohypophysis arises from ectoderm from the roof of the mouth, and the posterior pituitary or neurohypophysis arises from ectoderm that evaginates ventrally from the diencephalon early in gestation. The two ultimately fuse although they remain structurally distinct.

Pituitary function following brain injury is frequently disrupted.[9,10] The anterior pituitary is most vulnerable to injury, and this injury is often precipitated by elevated intracranial pressure, sustained hypotension, anoxia, and subarachnoid hemorrhage.[11] Growth hormone deficiency (GHD), hypogonadism, and hypothyroidism are the most common sequelae of pituitary injury following TBI.[11]

GHDs are implicated in cognitive dysfunction (attention, executive functioning, memory, and emotion), mitochondrial function, fatigue, dyslipidemia, reduced strength

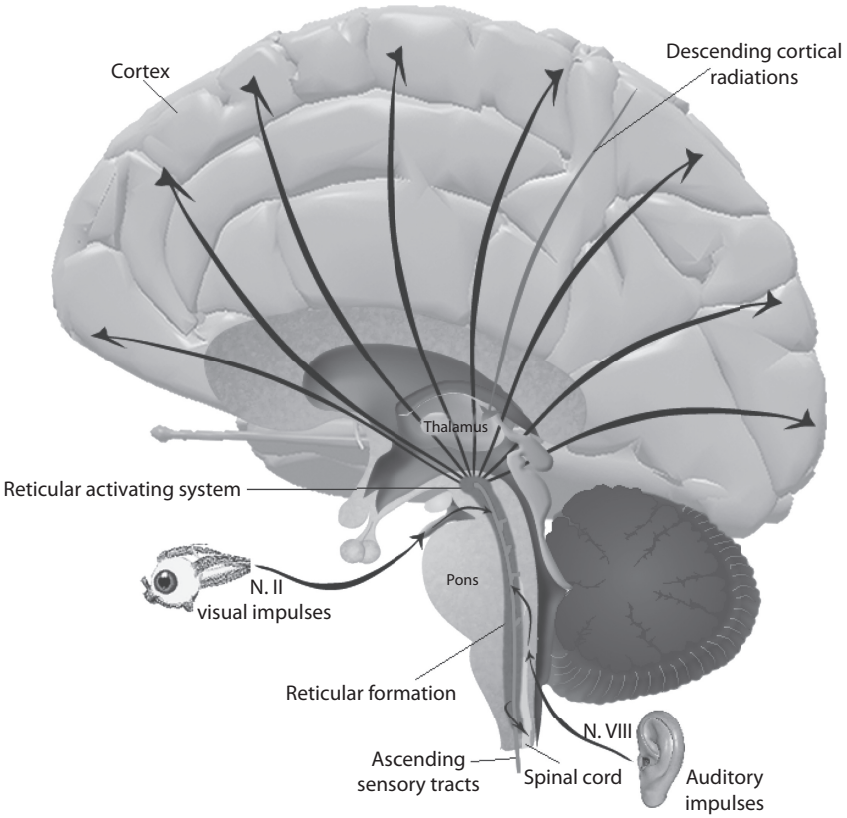


Figure 6.6 **(See color insert.)** Reticular activating system with sensory input, ascending and descending pathways.

and exercise capacity, and osteoporosis. Correction of GH has been suggested to benefit cognitive function postinjury.[12] Insulin-like growth factor-I (IGF-1) treatment has been shown to reduce demyelination and upregulate gene expression of myelin-related proteins in other populations[13] and may well play a role in recovery and/or preservation of function following brain injury. Six months of GH substitution in GHD individuals was found to improve long-term and working memory.[14] fMRI studies revealed activations in prefrontal, parietal, motor, and occipital cortices during a working memory task and less recruitment compared to placebo in the ventrolateral prefrontal cortex, suggesting overall less effort required and more efficiency in neural recruitment.[14] Others have reported improvements in attentional performance at 3 months and 6 months of GH treatment.[15] GH impacts mitochondrial function, and decreased levels may directly impact energy production in the cell body as well as along the axon and in axonal and dendritic end plates, where mitochondrial function is necessary in meeting energy demand throughout the cell.[16,17]

GH and IGF-1 may beneficially impact speed of information processing. GH is also implicated in myelin production in the CNS. In the presence of axonal injury in spinal cord injury models designed to simulate demyelinating disease, administration of IGF-1 increases myelin generation through increased myelin protein synthesis and myelin regeneration via oligodendrocytes.[13]

Thyroid function is crucial for normal brain development and for proper production of oligodendrocytes.[18–22] Further, thyroid administration early in a demyelinating inflammatory disease model enhances and accelerates remyelination, increasing expression of platelet-derived growth factor-α receptor, restoring normal levels of myelin-basic protein mRNA and protein, and allowing early and morphologically competent reassembly of myelin sheaths.[23] Thyroid is also clearly implicated in the regulation of mitochondrial function.[24]

Similarly, thyroid is implicated in enhancing remyelination in chronic inflammatory disease.[23] Thyroid and steroid hormones' impact on neural structures should be considered. Thyroid hormones regulates availability of cytoskeletal proteins necessary for neuronal growth.[25] Concentrations of thyroid hormone receptors have been found to be highest in the hippocampus, amygdala, and cerebral cortex of rats.[26] Depletion of thyroid hormones in adult rats results in a significant reduction in dendritic density in the cerebral cortex.[27,28] Thyroid function is crucial in normal brain development and impacts gene regulation for encoding proteins of myelin, mitochondria, neurotrophins and neurotrophic receptors, cytoskeleton, transcription factors, splicing regulators, cell matrix proteins, adhesion molecules, and proteins involved in intracellular signaling.[21] Many of these, if not all, play a role in recovery of neuronal and astrocytic function following brain injury. Excess and deficient levels of thyroid hormones can impact

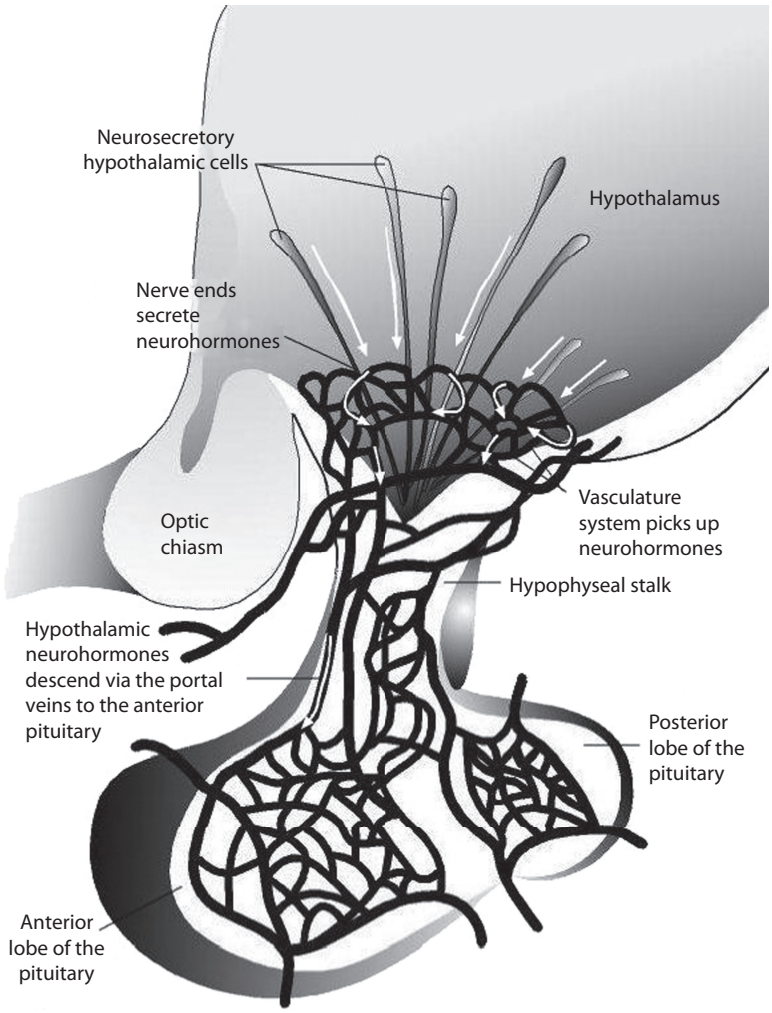


Figure 6.7 Hypothalamus, hypophyseal stalk, and pituitary showing anterior and posterior pituitary division and blood supply.

neurodevelopment.[18] Two iodothyronines (T3 and T2) have been shown to be effectors of the actions of thyroid hormones on energy metabolism and the regulation of energy-transduction performed by cellular mitochondria.[24]

Androgen deficiencies have clear implications for both cognition and mood. Sex steroid administration has been shown to be beneficial in improving working memory, particularly in men.[29] Estrogen has been shown to increase the number of synapses in the hippocampus in animals[30–32] and has been shown to improve verbal memory in women.[33,34] Estrogen has also been demonstrated to impact dendritic density as well as acetylcholine synthesis.[35,36] In fact, estrogen therapy has been shown to be effective in Alzheimer's disease.[37]

Glucocorticoid receptors are prominent in the limbic system.[27] As a significant portion of the information processing circuitry, in particular as it relates to the medial temporal lobe complex, the role of the limbic system is substantial in memory consolidation. The amygdala is important in mediating the influences of epinephrine, norepinephrine, and glucocorticoids on memory.[38]

THALAMUS

The thalamus is comprised of four groups of nuclei: the *anterior*, *medial*, *ventral*, and *posterior*.[39] The *anterior* nucleus is a single nucleus that receives its major input from the mammillary nuclei of the hypothalamus and the presubiculum of the hippocampal formation. It is interconnected with the cingulate and frontal cortices and may be involved in memory. The *medial* nucleus is comprised of the mediodorsal nucleus, which has three subdivisions. Each of these projects to a particular region of the frontal cortex, and input is received from the basal ganglia, amygdala, and midbrain. The medial nucleus is also implicated in memory. The *ventral* nucleus is comprised of the ventral anterior and ventral lateral nuclei. These are involved in motor control. Input to these nuclei comes from the cerebellum and basal ganglia, and output is to the motor cortex. The ventral posterior nucleus, also part of the ventral nucleus, sends somatosensory information to the neocortex. Last, the *posterior* nucleus is made up of the medial geniculate, lateral geniculate, lateral posterior nuclei, and pulvinar. The medial geniculate nucleus receives tonotopic auditory

stimulus and projects it to the superior temporal gyrus. The lateral geniculate receives information from the retina and projects it to the primary visual cortex.[39]

The nuclei discussed thus far are referred to as *specific thalamic nuclei*. Figure 6.8 provides a detailed depiction of thalamic nuclei, their connections, and functions. They project to specific primary sensory areas of the cortex. Nonspecific nuclei, on the other hand, project diffusely to several cortical and subcortical regions. The thalamus receives a great deal of input from the cortex. In fact, cortical input to the lateral geniculate nucleus, for example, is greater in number of synapses than input from the retina. Most thalamic nuclei are similar. A single thalamic nucleus sends information to multiple cortical areas, which return information back to the thalamus but to different thalamic nuclei. Irrelevant information is suppressed, and so-called "correct input" is facilitated by positive feedback via corticofugal projections.[40]

The thalamus is surrounded by the reticular thalamic nucleus, which forms an outer layer to the thalamus. The reticular nucleus uses the inhibitory neurotransmitter GABA, and most other thalamic nuclei utilize glutamate,

Anterior nucleus—Receives input from the mammillary nuclei of the hypothalamus and the presubiculum of the hippocampal formation. Connected with the cingulate gyrus and frontal cortices. Involved in memory.

Lateral dorsal nucleus—Inputs from the hippocampal formation and mammillary bodies and projects to the cingulate cortex. Relays signals to the cingulate gyrus. May contribute to visceral-sensory integration.

Lateral posterior nucleus—Inputs from adjacent thalamic nuclei. Interconnected with superior parietal lobe. Aids in integrating and transcoding multiple sensory modalities underlying higher mental functions.

Medial nucleus—Input from the basal ganglia, amygdala, and midbrain. Comprised of the mediodorsal nucleus which has three subdivisions. Each projects to a particular region of the frontal cortex. Implicated in memory.

Ventral anterior nucleus—Inputs from the basal ganglia and cerebellum. Outputs to the supplementary motor cortex. It initiates wanted movement and inhibits unwanted movement.

Ventral lateral nucleus—Input from the cerebellum and basal ganglia. Outputs to the primary motor cortex and premotor cortex. Aids coordination and planning of movement. Plays a role in learning movement.

Ventral posterior nucleus—Input from the medial and spinal lemniscus, and spinothalamic and trigeminothalamic tract. Outputs to the somatosensory cortex and ascending reticuloactivation system. Functions in touch, body position, pain, temperature, itch, taste, and arousal.

Medial geniculate nucleus—Receives tonotopic auditory stimulus and projects it to the superior temporal gyrus.

Lateral geniculate nucleus—Receives information from the retina and projects it to the primary visual cortex.

Pulvinar—Connection with visual cortical, somatosensory cortical association areas, and with cingulate, posterior parietal, and prefrontal cortical areas. Aids in language formation and processing and reading and writing.

Reticular thalamic nucleus—Forms an outer layer of the thalamus. Neurons terminate on other thalamic nuclei as they exit the thalamus. Exerts a modulator effect on the actions of other thalamic nuclei.

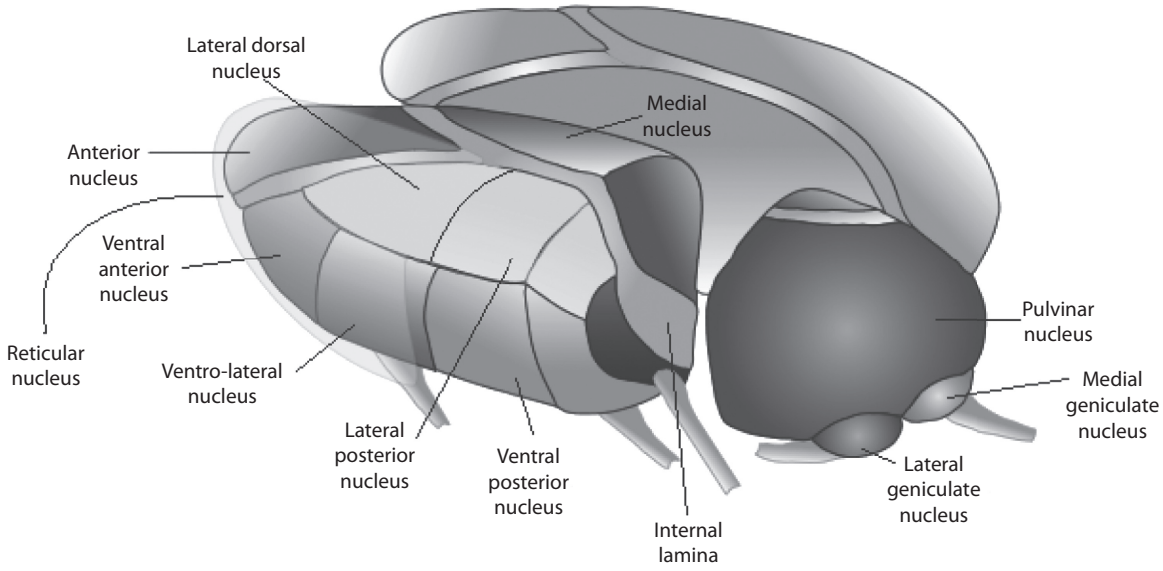


Figure 6.8 **(See color insert.)** Thalamic nuclei locations, pathways, and functions.

an excitatory neurotransmitter. Neurons of the reticular nucleus do not interconnect with cortical neurons, but terminate, instead, on other thalamic nuclei as they exit the thalamus. The reticular nucleus exerts a modulatory effect on the actions of other thalamic nuclei in this manner. As a result, a degree of information processing occurs at the thalamus due to the monitoring of the thalamocortical stream of information made possible by the collaterals of other thalamic nuclei synapsing on reticular neurons as they pass through the reticular nucleus' outer layer.[39]

BASAL GANGLIA

The basal ganglia are comprised of multiple subcortical nuclei: the *dorsal striatum* (comprised of the caudate nucleus and putamen), the *ventral striatum* (comprised of the nucleus accumbens and olfactory tubercle), the *globus pallidus*, the *ventral pallidum*, the *substantia nigra*, and the *subthalamic nucleus*. The *striatum* receives input from the cerebral cortex, thalamus, and brain stem and projects to the globus pallidus and the substantia nigra. The *globus pallidus* and *substantia nigra*, in turn, form the major output projections from the basal ganglia. The basal ganglia are involved in a variety of behaviors, including voluntary movement; sensorimotor coordination; response selection and initiation; and skeletomotor, oculomotor, cognitive, and emotional functions.[41,42] The caudate may be involved in selection of behavior based upon changing values of goals, knowledge of which actions lead to what outcomes, and goal-directed action via its connections with the frontal lobe.[43] Basal ganglia output is back to the cortex via the thalamus or to the brain stem. The basal ganglia serve as an important system linking the thalamus and cerebral cortex. Information that originates from a specific cortical area may be returned from the thalamus to other cortical areas.

MEDIAL TEMPORAL LOBE AND HIPPOCAMPAL COMPLEX

The medial temporal lobe (MTL) includes the hippocampal region (CA fields, dentate gyrus, and subicular complex), entorhinal, perirhinal, and parahippocampal cortices (Figure 6.9). The hippocampus has been widely studied due to its role in memory. The hippocampal gyri are located in the inferior medial temporal lobes.

Damage to the hippocampus or any of the association areas in the temporal lobe with which it connects will result in deficits in explicit memory.[29–31] Explicit memory is sometimes referred to as *declarative memory* and includes

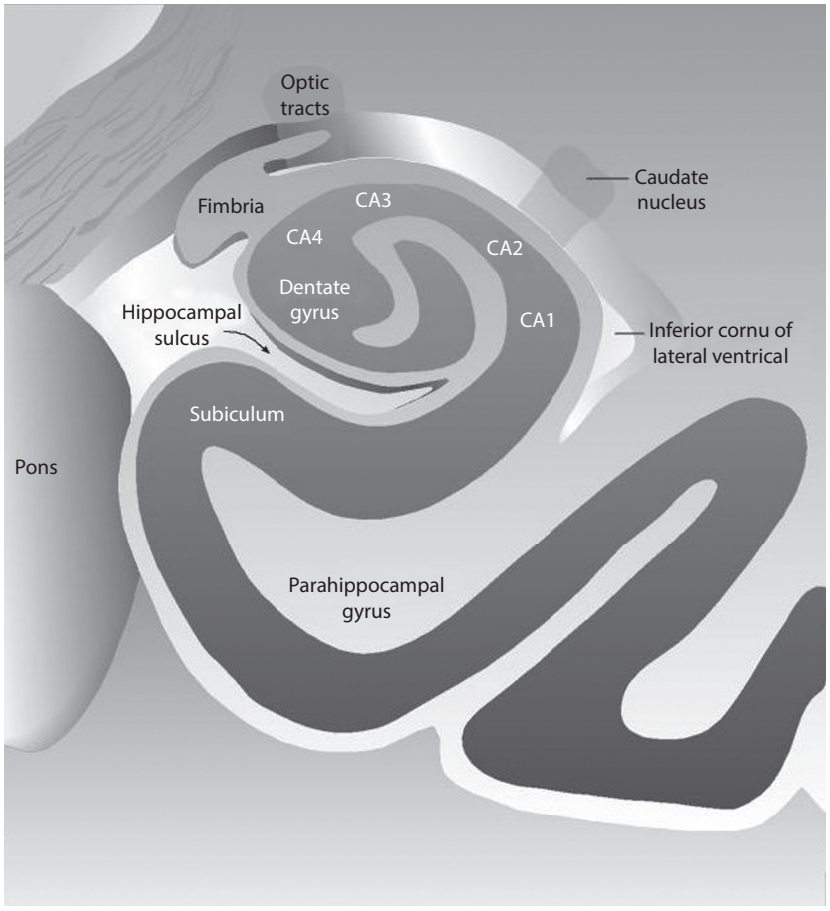


Figure 6.9 Coronal view of hippocampal complex.

episodic and semantic memory. Declarative memory formation is impaired following MTL damage. Semantic memory is the capacity for acquisition and recollection of facts and other general knowledge about the world.[44–46] Episodic memory involves memory for events and experiences, and semantic memory involves memory for factual information abstracted from specific incidents or episodes.[47,48] Characteristics of declarative memory include that it is flexible, consciously accessible, and integrated into a broad fund of stored knowledge.[49–52]

As damage in the MTL extends laterally, semantic knowledge becomes increasingly impaired. Formation of declarative knowledge may not be possible with complete MTL damage even with the support of structures outside the MTL.[53] New episodic and semantic memory formation will also be impaired. Processing of novel versus familiar auditory stimuli appears to activate the anterior and posterior hippocampal complex, respectively, and processing of novel versus familiar visual information appears to be reversed.[54] Likewise, there appears to be a differential response for encoding and retrieval activity with the anterior structures responding more to encoding while the posterior structures respond more to retrieval.[55,56]

Information appears to be first processed in the association areas of the prefrontal, limbic, and parieto–occipital–temporal cortices.[47,57] Information is then passed to the parahippocampal and perirhinal cortices and, from these, on to the entorhinal cortex. From the entorhinal cortex, information passes to the dentate gyrus, the subiculum, and the CA3 and CA1 regions of the hippocampus. The dentate gyrus passes information to the CA3 hippocampal region, which then passes information to the CA1 region and on to the subiculum. From there, information is sent back to the entorhinal cortex,[58] on to the parahippocampal and perirhinal cortices, and back to the cortices. Hippocampal projections to cortical areas are widely distributed.[58] The circuitous nature of these connections provides support for a role in detection of novel stimuli,[59,60] associative memory,[61,62] encoding of explicit memory,[60] retrieval of explicit memory,[63] attentional control of behavior,[64] spatial memory,[65,66] and possibly a role in the development of long-term memory.[47] The CA3 region of the hippocampus appears to deal primarily with previously stored information. The CA1 region, in contrast, seems to deal primarily with novel information. The CA3 region is hypothesized to provide sparsely encoded information arising from highly processed information received from the dentate gyrus.[67–69] The CA3 is also thought to be an autoassociator and comparator.[67–69] It appears that CA3 may be able to retrieve entire patterns from partial or degraded input, comparing it with data arriving from the entorhinal cortex and, thereby, acting to filter information sent to CA1.[70] Processing of spatial scenes appears to involve the parahippocampus, and spatial memory involves the right hippocampus. Context-dependent explicit memory is more dependent upon the left hippocampus.[66]

The connection of the association cortices and hippocampal structures is quite important for overall cognitive function. Information from several, widely distributed cortical regions must be integrated to perform complex mental functions. The association areas receive information from higher-order sensory areas and, ultimately, convey the consolidated information to higher-order motor areas.[71] The motor areas organize planned actions. The hippocampal role, together with involvement of other medial temporal and limbic lobe structures, is found in the manner in which hippocampal input is received from and output is projected to the associative cortices. These circuits appear to be active in processes whereby previously stored information is modified by new experience.[47]

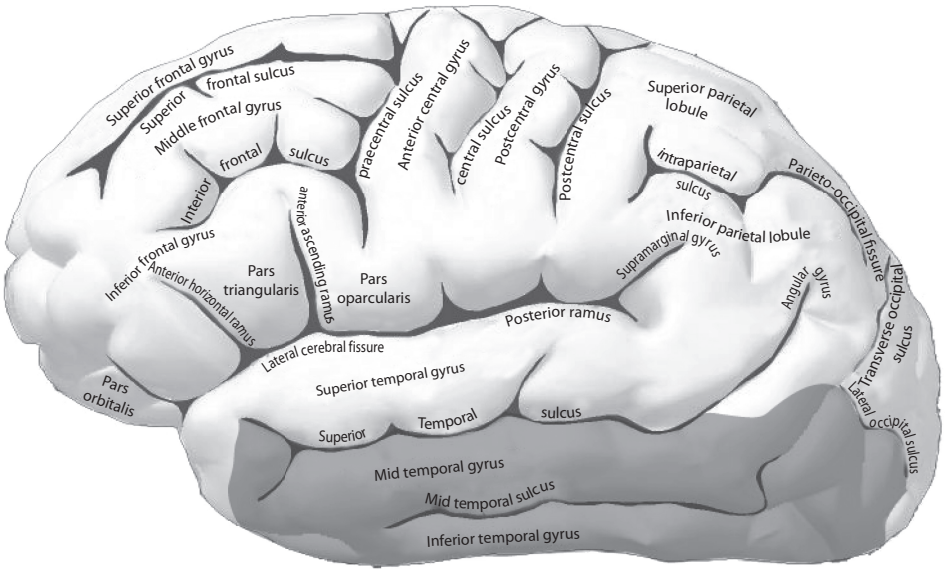
Hippocampal efferent projects to the amygdala, the septum, the fornix, the thalamus, the mammillary bodies, the medial preoptic area, and the perifornical nucleus of the hypothalamus.[72] The anterior hippocampus appears to exert an excitatory modulatory effect on the amygdala.[73] It exerts inhibitory effects on the fornix and both excitatory and inhibitory effects on the ventromedial nucleus of the hypothalamus. The amygdala is implicated in self-preservation activities, such as the search for food, feeding, fighting, and self-protection[74] and the association of sensory information with emotional states. McGaugh[75] cites evidence that the basolateral region of the amygdala is crucial in memory consolidation arising from emotionally impactful experience. Stress hormone production and other neuromodulatory systems activated by such experiences are made possible via the anterior hippocampal projections to the amygdala, which progress to the hypothalamus and the basal forebrain. The posterior hippocampus also sends projections to the hypothalamus via the fornix. Motivational significance of incoming stimuli is determined by the amygdala with subsequent coordination of multiple systems to enable an appropriate response.

Long-term potentiation (LTP) occurring in the hippocampus serves as a component of synaptic consolidation. LTP in the hippocampus is largely dependent upon dopaminergic availability.[76] Some authors suggest dopamine receptor (D1/D5) activation serves to initiate intracellular second messenger accumulation, functioning more in a modulatory role.[77] There actually may be a synergistic role between D1/D5 receptor activation and *N*-methyl-D-aspartate (NDMA) receptor activation for LTP induction.[78]

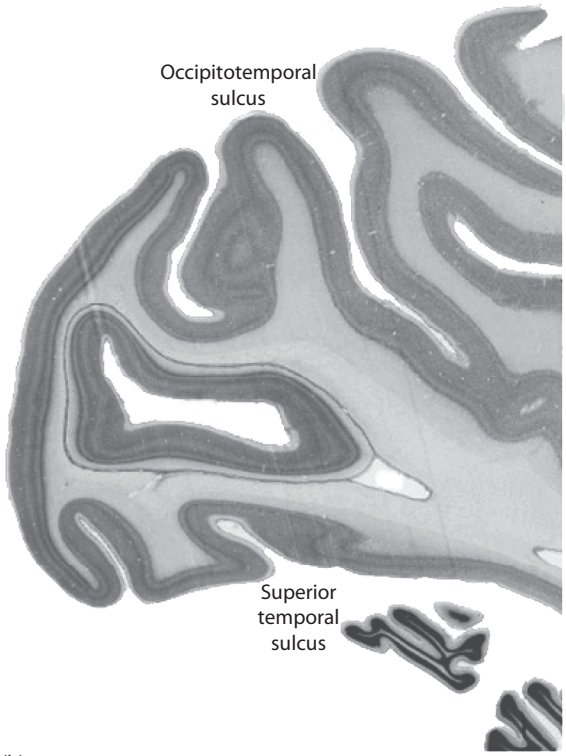
INFERIOR TEMPORAL LOBE

The inferior temporal cortex includes the inferior and middle temporal gyri and is boundaried, posteriorly, just anterior to the lateral occipital sulcus and, anteriorly, just a couple of millimeters posterior to the temporal pole. It extends laterally to the occipitotemporal sulcus (Figure 6.10a and b).

The inferior temporal lobe (ITL) interconnects with the visual peristriate cortex (V2, V3, V4) and the polysensory areas of the superior temporal sulcus, the temporopolar



(a)



(b)

Figure 6.10 **(a)** Lateral view of inferotemporal cortex. **(b)** Coronal view of occipitotemporal and superior temporal sulci.

prosiocortex, the prefrontal cortex (PFC), and the limbic system (comprised of the limbic lobe, hippocampus, and amygdala). (For a detailed review of ITL anatomy in the primate, see Logothetis.[79]) Due to its interconnections, it is structurally predisposed to integrate multiple aspects of vision, relay information to multisensory convergence areas, and interact with structures that play an important role in decision making, short- and long-term memory, and emotions.[79]

The ITL appears to be important for object recognition and categorization. Category-specific impairments have been tied to temporal lobe–specific injuries.[80] Visual features that are important in category membership determination are instantiated in single neuron activity in primate ITL,[81] and neuronal selectivity for shape and color have been demonstrated.[82] It appears that short-term memory for the categorized visual percept of pictures is represented in the ITL.[83] ITL involvement includes sensitivity to the level of categorization and the level of expertise of the observer.

The ITL in primates has been shown to be involved in visual discrimination,[84–87] visual attention,[84,88] and visual

short-term memory.[88–90] Stimulation of the ITL in humans results in recall of visual imagery.[91] Selective reactivity to stimulus dimensions of shape, orientation, and color has been demonstrated in single unit recordings in the ITL.[92–94] Additionally, evidence has demonstrated modulation of ITL unit response by attention and situational variables.[95–97] The ITL does not appear to be directly involved in association memory in that neurons have not been found to discriminate on the basis of reward.[95] Performance of serial recognition tasks (in which intervening stimuli occur between novel and familiar presentations) is associated with the ITL.[98]

Thomas et al.[82] found that approximately 25% of sampled ITL neurons responded to only specific category exemplars during a visual categorization task. The exemplar specificity of ITL neurons may point to a larger role to be played by the PFC in categorical boundary determination. The majority of sampled neurons in the ITL were not category specific and appeared to be "broadly tuned" instead for categorization activity. Unlike individual neurons in the PFC that are able to encode rules, neurons in the ITL do not appear able to respond individually to derive categorization but rather function collectively.

FRONTAL LOBE

The frontal lobe is organized to provide motor function in the primary motor cortex (Brodmann 4) anterior to the central fissure. The primary motor cortex receives its input from the premotor cortex (areas 6 and 8) and from the somatosensory cortex. Fibers from areas 4, 6, and 8 of the frontal lobe and 3, 2, and 1 of the parietal lobe contribute to the corticospinal tract. Horizontal gaze is controlled by area 8. The motor component of speech is managed by areas 44 and 45 in the left hemisphere (Figure 6.11).[99] The balance of the frontal lobe, comprising nearly two thirds of the entire frontal lobe, provides support for executive cognitive functions. Information flow in the postcentral fissure cortex progresses from primary to secondary to tertiary association cortices. However, that information flow is reversed in the frontal lobe with flow progressing from tertiary to secondary to primary motor cortices. In fact, the frontal lobe is largely informed by postcentral fissure and subcortical structures.

The PFC is the highest order of neocortex in both phylogenetic and ontogenetic terms and represents about one third of the neocortex. It is the latest maturing in myogenic and synaptogenic terms[100–102] and does not reach full maturity until young adulthood in humans.[103–105] The PFC is crucial for propositional speech, reasoning, motor and executive memory, temporal organization of behavior, mediation of contingencies of action across time, retrospective (short and sensory memory) and prospective memory, active adaptation to the environment, skeletal and ocular movement, reasoning, spoken language, modulation of visceral actions, and emotional behavior.[106,107] The PFC can be subdivided into three major regions: orbital, medial, and

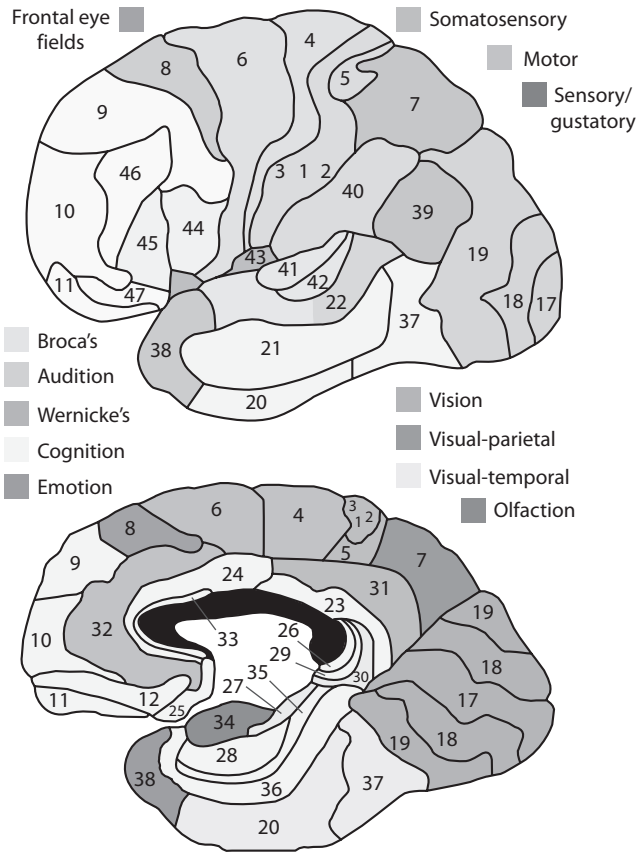


Figure 6.11 **(See color insert.)** Brodmann areas color-coded for primary functional significance. (From Prof. Mark W. Dubin, University of Colorado–Boulder, MCD Biology, http://spot.colorado.edu/~dubin/talks/brodmann/brodmann.html. Reprinted with permission from M. W. Dubin.)

lateral. The orbitofrontal cortex provides inhibitory control via its efferent to the hypothalamus, the basal ganglia, and other neocortical areas, some of which are within the PFC itself. Damage to the orbitofrontal cortex results in behaviors described as impulsive, disinhibited, irritable, contentious, tending toward coarse humor, and showing a disregard for social and moral principles.[108]

The medial PFC includes the most anterior portion of the cingulate gyrus. It is involved in attention and emotion. Damage to the medial frontal cortex can result in difficulty in initiating movement or speech[109,110] and akinetic mutism in larger lesions. Apathy, abulia, or a loss of spontaneity can be seen together with difficulty in concentration on behavioral or cognitive tasks.[108]

The lateral PFC is important to organization and execution of behavior, speech, and reasoning. Luria found damage to this area to be associated with inability to formulate and carry out plans and sequences of actions[111] and conscious representation and construction of sequences of spoken and written language.[112] Damage in the lateral PFC is often accompanied by severe attention disorder.

Afferent connections to the PFC include the brain stem, thalamus, basal ganglia, limbic system, amygdala,

hypothalamus, hippocampal association cortices, and each of the other prefrontal regions but not primary sensory or motor cortices. The prefrontal regions are connected both to themselves and to each other with some cortical connectivity being interhemispheric.

It is reasonable to compartmentalize information collection and retention as primarily a posterior cortical function while formulation and execution of actionable concepts and events or refinement of previous knowledge is the purview of the anterior cortical structures. The memory networks of the posterior cortex acquire information and associations with action and forward that information to the PFC to influence the formation of networks of executive memory.[108]

Neuronal networks that serve perceptual memory are found in the postcentral fissure area and are organized hierarchically upon the primary sensory cortices. The precentral fissure region of the PFC serves executive memory and provides an organization system of movement, behavior, speech, and reasoning based upon a similar hierarchy of inputs from disparate cortical and subcortical structures. The PFC utilizes these structures as afferent sources of information in addition to efferent networks to achieve the desired behavioral, speech, or reasoning outcome.[108,113] Higher cortical areas accommodate higher orders of memory, including episodic and semantic memory, together constituting declarative memory. Individual items of memory or knowledge are less hierarchically arranged and are better thought of as relying upon mixtures of information from mixed memory types. Memory of a specific event relies upon a network of structures serving each of the mixed memory types.

Information flow in the CNS appears to utilize either primary or associative cortices, depending upon the degree of familiarity or novelty of the information. As novel information arrives and is compared with previously acquired information, comparative assessment appears to be conducted by the hippocampus and associative cortices acting in harmony. Previously acquired information both impacts and is impacted by the utilization of novel information. The posterior cortices appear to function as increasingly effective information processing and storage centers, providing information necessary for anterior cortical processing, such as executive function. Novel information requires the largest utilization of cortical resource due to heavy recruitment of multiple primary sensory areas. Once the information is learned, much less cortical resource is utilized, and the information appears to be more efficiently represented in smaller cortical areas of associative cortex. As new information arrives that bears upon previously acquired information, these networks are activated and modified to represent and assimilate the newly acquired information. This resource utilization pattern, from more to less cortical resource, can also be seen in studies examining cortical activation patterns during phases of skill acquisition.[114,115]

The prefrontal networks appear to function by prefrontal neuronal control exerted over existent networks. The neurons of the PFC can also substantially modify previously acquired information. Neuromodulatory biasing of the network connections to address requisite needs in problem solving, reasoning, and other executive functions has been proposed. Neurons within the PFC provide biasing signals that guide the flow of neural activity along pathways to establish the proper interaction between inputs, internal states, and needed outputs for a given task.[116] The PFC appears to exert cognitive control in a top-down fashion upon existing networks, biasing them into controlled activity and disallowing their activity outside of the constraints of the current situation. The PFC marshals the same information and action networks that function to provide automaticity of response, however, through the neuromodulatory biasing of the network, it disallows reflexive or automatic responses and promotes the creation of event-specific responses that may be partially or entirely new.

Neurons in the PFC have been found to be individually capable of encoding abstract rules.[117] The PFC appears to be involved in guidance of behavior according to previously learned rules and in utilization of working memory.[118] Because the PFC receives highly processed information from other parts of the brain, its role appears to be to synthesize that information into learned task contingencies, concepts, and task rules.[119] PFC neurons are able to maintain task-relevant information and have a strong ability to resist interference from distraction.[113,120–122]

COMMISSURAL AND ASSOCIATION TRACT FIBERS

Information must be moved from one cerebral area to another. Transport between subcortical and cortical areas is accomplished by projectional fibers, which comprise the internal capsule. Fibers of the internal capsule carry information both toward and away from the cortex. Axons of the internal capsule spreading out to all areas of the cortex are known as the *corona radiata*. Fibers from the thalamus projecting to the cortex travel in the internal capsule. Projections from the anterior and medial thalamic nuclei carry visceral and other information and project to the frontal lobe via the anterior limb of the internal capsule. Projections from the ventral anterior and ventral lateral nuclei of the thalamus travel in the genu and posterior limb of the internal capsule and reach the motor and premotor areas of the frontal lobes. The ventral posterior and medial thalamic nuclei project to the sensory cortex of the parietal lobe via the fibers of the posterior limb of the internal capsule. The posterior limb of the internal capsule also contains optic and auditory fibers. Corticobulbar (head and face muscles) and corticospinal (neck and trunk muscles) motor pathways travel via the posterior limb of the internal capsule to the brain stem (corticobulbar) and spinal cord (corticospinal).

Interhemispheric connections are accomplished by the corpus callosum and two smaller commissural bundles. The anterior commissure interconnects the anterior temporal areas. The hippocampal gyri are connected to each other via the hippocampal commissure.

Intrahemispheric interconnection is accomplished by association fibers. The temporal and frontal lobes are joined by the uncinate fasciculus. The medial surfaces of the frontal, temporal, and parietal lobes are connected by the cingulum, which also connects the cingulate gyrus to the orbitofrontal cortex and the hippocampal cortex. Projectional fibers from the thalamus to these regions are contained in the cingulum. The anterior cingulate gyrus is implicated in executive attention[123] through the detection of conflicts occurring during information processing that signal the need to engage top-down attentional processes.[124] The anterior cingulate cortex is active in conscious attention during auditory processing.[125] It may provide an important connection between widely disparate aspects of attention, such as the mental operations of visual target detection and semantic content by integration of information arising from the various multimodal association cortices. The anterior cingulate gyrus has been implicated in episodic memory retrieval as well.[126] Finally, *arcuate fibers* connect adjacent gyri in neocortical areas. An excellent review of commissures, long tracts, and pathways connecting cortical and subcortical areas is provided by Taber and Hurley.[127]

Widespread/diffuse traumatic axonal injury (TAI) is a common characteristic of nearly all traumatically induced brain injury.[128] TAI impacts cortical and subcortical pathways that serve the distributed network of discrete cortical regions in which features that define an object or experience are stored. Both storage and recall of information are necessarily impacted by TAI and made less efficient. TAI is most frequently seen in the long tracts of the midline structures of the brain.[129] The cingulum is thought to be an important structure in the transfer of information from distributed regions of the brain to association cortices for integration. As such, the prevalence of TAI in the regions of the brain surrounding the cingulum will necessarily impact information transfer.

PRINCIPLES OF NEUROPHYSIOLOGY AND COGNITION

The study of cognition has long been the realm of experimental psychology. Carefully designed research and detailed behavioral observation allowed insight into phenomena, such as sensitization and habituation. The limitations of psychological investigation, however, rarely allowed for much beyond conjecture as to the nature of the physiological underpinnings of such behaviors. Cognitive processes, such as memory, have long been investigated, and early information regarding neurophysiological issues arose from observation of persons with known injuries who may have been later studied at autopsy to attempt to correlate, in gross anatomical terms, sites of lesion and observed premorbid behavioral changes.

Advances in neuroscience continue to expand information available regarding neurophysiological function and the cognitive processes that arise from that function. It is now possible to discuss neuronal function and neurotransmission at the level of the cell, gene, ion, and neurotransmitter. Neuroanatomical organization has advanced considerably from the early days when primary debate consisted of whether nerve cells interconnected via a protoplasmic continuity or whether nerve cells existed individually and were contiguous rather than continuous.[58]

As neuroscience continues to expand available information, conceptions about neurocognitive function will likewise be necessarily advanced and refined. It is important to utilize available information, however incomplete it may still be, to develop rational theoretical constructs from which diagnosis and treatment of cognitive function is approached.

INFORMATION PROCESSING, NEUROTRANSMISSION, AND LEARNING

Information processing has long been conceived as dependent upon the existence of three levels of storage: sensory stores, short-term memory, and long-term memory. Baddeley's early conceptualization of these mechanisms led to the question of how information was transferred from short-term storage (STS) to long-term storage (LTS).[130] Others have more recently suggested a need to revisit these concepts to consider frontal lobe structure which may enable (1) the updating and maintenance of information; (2) the selection, manipulation, or monitoring of information; and (3) the selection of processes, subgoals, or planning.[131]

Memory consolidation implies a progression of staging of memory with variations in strength and reliability of memories across time. Consolidation occurs at the synaptic level and the systemic level. Much has been done recently to investigate the biological mechanisms of memory consolidation. Synaptic tagging was identified as a factor in the synaptic consolidation process whereby requisite proteins for protein synthesis necessary for LTP accumulate in confined regions within the dendrite until LTP is instituted.[132,133] Genetic networks have been identified that, through upregulation or downregulation, are active in memory consolidation and memory retrieval and are necessary constituents in both.[134] Memory is most recently viewed as a complex biological process whereby networks of neurons and genes function as the neurophysiological basis for memory.[134] Genetic alteration in response to memory formation may be considered at both the synaptic and systemic levels of consolidation. At the systemic level of consolidation, information is stored in places other than the originally implicated synapses. Information is also altered once stored in systemic consolidation, seemingly comprised of a more synapse-efficient process.

At a cellular level, it has been demonstrated that different types of memory formation place different demands on the cellular mechanisms for protein synthesis. Protein synthesis occurs within the nucleus of the neuron in direct response to learning. Protein synthesis does not occur, however, for all types of memory. STS does not require protein synthesis. "All of the proteins, including receptors, ion channels,

enzymes, and transporters, required for short-term memory formation and temporary storage are already present in sufficient abundance. In sharp contrast, however, long-term memory absolutely depends on the synthesis of new proteins or the increased synthesis of already existing proteins."[135]

Synaptic activation and transmission lead to changes throughout the neuron. The nucleus, axon, dendrite, and synapse undergo structural changes that support information processing, learning, and memory. Changes at the synapse are such that they support the immediate, short-term, or long-term demands of the information processing process and either encourage or discourage further synaptic transmission. When transmission occurs across a synapse, the synapse becomes "potentiated," thereby making the synapse more responsive to the next transmission.[136] Potentiation of the synapse can be of varying durations, lasting seconds to years. Posttetanic potentiation (PTP) lasts for a minute or less, and short-term potentiation (STP) lasts somewhat longer. PTP and STP result from increases in the number of quanta released and/or the strength of their postsynaptic effects.[50] LTP lasts weeks to years. LTP requires several simultaneous signals to be received by the neuron and effectively "strengthens" the synapse.

However, LTP alone does not provide adequate support for learning that is preserved over a lifetime. Declarative memory formation is highly dependent upon MTL structures including the hippocampus and entorhinal, perirhinal, and parahippocampal cortices. These structures are crucial for information acquisition and STS; however, their role dissipates over time as information is transferred from recent storage to LTS.[137] In the latter instance, information appears to be distributed to other neocortical areas where it is stored.

LTP has an inhibitory counterpart known as *long-term depression* (LTD). LTD, a decrease in synaptic responsivity that is activity dependent, has been found to be induced postsynaptically, and it is possible that LTD may also require the production of a retrograde messenger.[138] Both LTP and LTD are viewed as cellular mechanisms involved in learning and memory. Habituation and sensitization are nonassociative types of learning and can be both short- and long-term in nature. Habituation and sensitization may be subserved by STP, LTP, and LTD.[139]

In studies with *Aplysia*, Frost et al.[139] demonstrated that STP and LTP were dependent upon the presentation of serotonin (5-HT). A single presentation of 5-HT resulted in an increase in the excitatory postsynaptic potential between the sensory and motor neuron that lasted minutes. Presentation of five applications of 5-HT resulted in an increase in the excitatory postsynaptic potential that lasted 24 hours, required new RNA and protein synthesis, and involved the growth of new synaptic connections between the sensory and motor neuron. It is important to note that 5-HT is the modulatory neurotransmitter for the studied sensory-motor synapse in *Aplysia*. A number of studies have demonstrated, with differing species, similar mechanisms underlying learning and the development of nondeclarative motor skills and explicit (hippocampus-based) memory.[140–142]

In instances in which LTP occurs, changes occur within the cell body and in gene expression. These changes may impact the function of all synapses or may be restricted to specific synapses. In instances in which only select synapses undergo LTP, other synapses of the same neuron are more readily able to undergo LTP due to changes in the genetic expression at the cell body. Castelluci et al. noted that both genetic expression and protein synthesis, not necessary for formation of short-term memory, likely were required for acquisition of long-term memory.[143] Additionally, it has been determined that neurotransmitters not only serve transmission of a signal across a synapse but also function in the regulation of local protein synthesis, independent of the cell body used to establish synapse-specific changes in synaptic strength.[144] Frost et al.[145] found underlying circuit modification could be accomplished by at least four neuronal sites for short-term memory formation in *Aplysia*. Martin et al.[144] later demonstrated that local protein synthesis occurred at the synapse independent of the soma and its nucleus, thereby allowing for long-term, branch-specific facilitation.

LTP has been shown to last for varying periods of time throughout the brain. Within the dentate gyrus, LTP can last for months and up to a year.[146] LTP within the hippocampal area of CA1 and in the neocortex can last weeks.[147,148] LTP has at least two phases: a protein synthesis-independent phase and a protein synthesis-dependent phase. The protein synthesis–independent phase can last a few hours while the protein synthesis-dependent phase lasts longer. Information that has passed into the protein synthesis-dependent phase is more resistant to loss. LTP can be more easily reversed early after its induction and becomes much less so 1 to 2 hours postinduction.[149] The development of resistance to reversal of LTP can be blocked by protein synthesis inhibitors.[150]

Reversal of LTP can be induced by transient anoxia,[151] low-frequency stimulation,[152,153] heterosynaptic high-frequency stimulation,[154] and seizure activity.[155] Brief exposure to novelty can result in a time-dependent reversal of LTP[156] and longer periods of exposure to novel enriched environments have been shown to gradually reverse LTP.[146] Abraham and Williams suggest that protein synthesis-dependent LTP may not permanently "lock in" a memory, but may simply act to raise the threshold for future change.[149]

Immediate-early genes (IEGs) have been identified that function in activity-dependent plasticity of dendrites.[157] The existence of IEGs (1) may account for rapid LTP formation that could not be accounted for by protein synthesis dependence alone, (2) may contribute to the protein synthesis-independent phase of LTP formation, and (3) are experience-dependent. IEG expression has been demonstrated within both hippocampal and neocortical neurons. IEGs do not require *de novo* protein synthesis or previous activation of any other responsive genes. IEG transcription initiates following patterned synaptic activity that induces long-term synaptic plasticity.[158,159] Limitations of protein synthesis inhibitors used to study LTP and protein synthesis led one group to investigate IEGs as potential participants in memory formation.[134]

One of these IEGs, *Arc* (activity-regulated cytoskeleton-associated protein), has been implicated in the encoding process.[160] *Arc* was initially investigated as a growth factor that, when stimulated, induced rapid and transient expression of a set of genes, IEGs, which encoded transcription factors, cytokines, and other molecules that are believed to regulate long-term cellular responses.[161] Others have found that similarly rapid genomic responses are induced in neurons by neurotransmitter stimulation.[162,163] The IEG, *Arc*, is induced in response to neuronal activity. It is involved in synaptic and proteomic responses of memory formation.[134] Interestingly, *Arc* transcription is induced by NDMA receptor activation that causes excitatory synaptic activity.[157,164] It should be recalled that a synergistic effect has been identified between dopamine and NMDA activation during LTP.[78] *Arc* is of interest because it was first found to be induced within 1 to 2 minutes of maximal electroconvulsive seizures (MECS) and was found as intranuclear foci within most neurons. It disappears within about 15 minutes and subsequently becomes prominent in cytoplasmic and dendritic regions from 15 to 45 minutes poststimulus. Later, *Arc* can only be found in dendritic regions. Studies show that *Arc* can be behaviorally induced in the hippocampus following the same time patterns observed following MECS.[160] Finally, *Arc* is expressed after exploration of an environment and in learning tasks in vivo.[70,160,165]

Gene expression is just one factor active in determination of a neuron's range of responses in recruitment or in stabilization of a neural circuit.[134] Memory formation depends then, at least, upon neural circuits and patterns of gene expression within individual neurons at any given time.

Although these studies are exciting in their implications, LTP and IEGs are not the only substrates of memory.[166] LTP, by itself, cannot account for all aspects of potentiation. The role of adhesion chemistry has been proposed by Lynch[166] as responsible for explanation of the time constraints observed for LTP and memory function. Three transmembrane cell adhesion receptors have been identified: *integrin*, *cell adhesion molecules*, and *cadherins*. "Integrin activation/engagement thus emerges as that process whose temporal requirements dictate the particular time courses recently discovered for LTP and repeatedly described for memory."[166]

Other morphological changes are known that may subserve LTP. Schubert[167] found that synaptic cleft modifications occur following synaptic transmission. Following repeated transmission across a synapse, the size of the synaptic cleft is reduced, and glycoproteins released into the cleft act to bind the synaptic end plates closer together. Additionally, the synaptic end plates themselves broaden, resulting in greater exposure of neurotransmitter vesicles. The result is more rapid release of neurotransmitter into the synapse and less distance for the neurotransmitter to travel. As more rapid release and uptake of neurotransmitter occurs, more rapid transmission occurs.

Neurons are organized in adjacent columns of cells within the CNS. Cells within columns serve separate but similar functions, and greater numbers of computational columns are correlated with area size of the cortex dedicated to specific function.[8] Activation of a single neuron can cause increased electrical activity in adjacent cells and may cause a focal neuronal LTP response.[168] Aggregate groups of neurons are thought to function most probably together.[169] Activation of adjacent cells within columns may facilitate a desired level of processing or compound information processing. Both nitric oxide and carbon dioxide have been identified as retrograde messengers in neurotransmission and may play a role in widespread LTP.[170] Nitric oxide is a relatively short-acting neurotransmitter. Its release has been demonstrated to be experienced by closely adjacent synapses,[168] and it has been implicated in reference memory in studies of working versus reference memory in rats.[171,172]

Simple neural activation is not sufficient to bring about certain morphological changes. *Reactive synaptogenesis* has been demonstrated to occur only when the neural activation is associated with learning.[173,174] During this process, new dendritic spine formation occurs at the synaptic level following repeated neurotransmission. This process is fairly rapid with studies showing it to occur within 10 to 15 minutes.[175] Synaptogenesis must be supported by both glial cells[176] and adequate blood supply.[173] The time frame required for synaptogenesis to occur may be more than coincidental to the time required to allow for the transport of requisite proteins, which must transpire in order to allow for information to be transferred to LTS.

Neuromodulatory neurotransmitters

Modulatory neurotransmitters play a major role in information processing. These substances most probably allow for a biasing of cortical and subcortical responsivity that is situationally determined.[116] The six primary modulatory neurotransmitter systems consist of the *noradrenergic* (norepinephrine), *adrenergic* (epinephrine), *dopaminergic*, *serotonergic*, *cholinergic*, and *histaminergic* cell groups. In addition, there are more than 50 neuroactive peptides that act as neurotransmitters although not all are active, of course, within the brain.

A nucleus of interest in the noradrenergic system is the locus ceruleus (blue spot) located dorsally and lateral of midline in the periaqueductal and periventricular gray matter of the pons, near the fourth ventricle in the rostral pons. Noradrenergic neurons (Figure 6.12)[179] are also located within the lateral tegmental area of the pons and medulla. Ascending projections from both regions reach the entire forebrain, the brain stem, cerebellum, and spinal cord, thereby impacting the entire CNS. Noradrenergic neurons of the medulla project to the hypothalamus, controlling endocrine and cardiovascular function. Those in the caudal regions of the pons and medulla are involved in sympathetic functions, such as blood pressure control.[177] The locus ceruleus is implicated in maintenance of vigilance and responsiveness to unexpected stimuli. The norepinephrine system is involved in modulation of attention, sleep–wake states, and mood. Although firing of the locus ceruleus increases

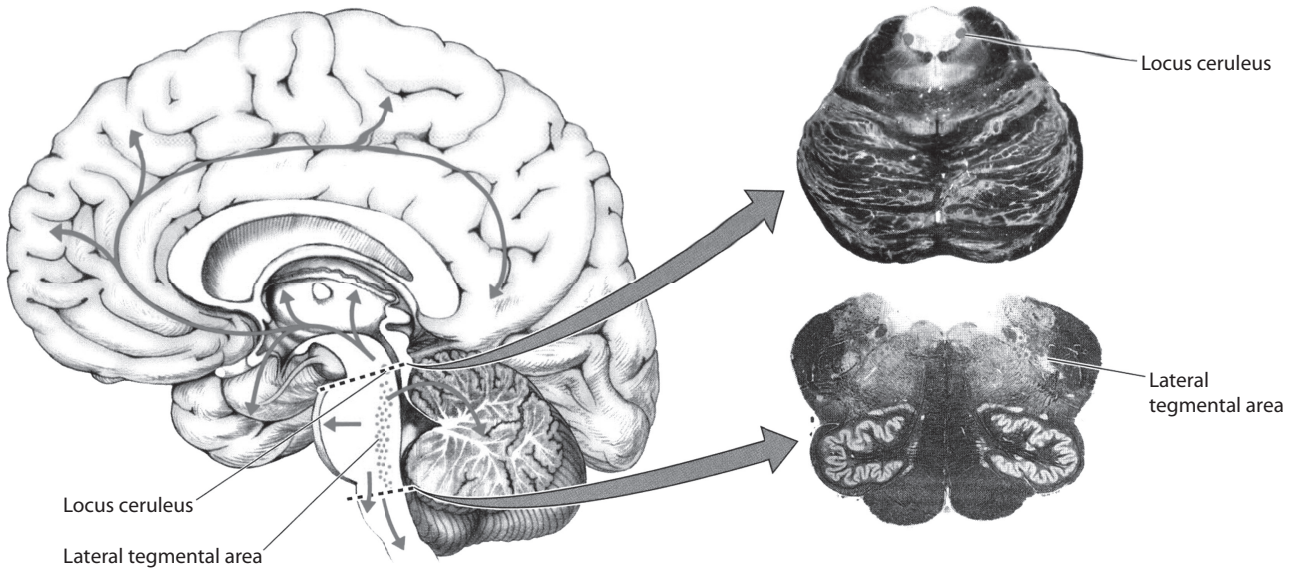


Figure 6.12 **(See color insert.)** Noradrenergic projection systems. (Line drawing from Blumenfeld, H., *Neuroanatomy through Clinical Cases*, Sinauer Associates, Inc., Sunderland, MD, 2002, p. 596. With permission from Sinauer. Photograph from Martin, J. H., *Neuroanatomy: Text and Atlas*, 2nd ed., Appleton & Lange, Stamford, CT, 1996, pp. 512, 520. Reprinted with permission from McGraw-Hill.)

during waking and decreases during sleep, lesions of the locus ceruleus do not cause somnolence. Norepinephrine is implicated in depression, manic-depressive disorders, obsessive-compulsive disorders, and anxiety disorders together with serotonin.[177] These cell groups constitute the long projection system of the reticular formation.[178]

Dopaminergic projections (Figure 6.13) arise from the substantia nigra pars compacta and the ventral tegmental area of the brain stem and traverse many systems. Dopaminergic neurons project to the telencephalon. Neurons project to the frontal and temporal cortices as well as to the striatum, the limbic cortex, the amygdala, and the nucleus accumbens. These structures are involved in emotion, memory storage (encoding, retrieval, and working memory), movement, initiation/initiative, and thought.

Dopaminergic projections travel via the tuberoinfundibular, mesostriatal, mesocortical, and mesolimbic dopaminergic pathways. The tuberoinfundibular pathway projects from the hypothalamus to the pituitary. The mesostriatal pathway arises from the substantia nigra and serves the striatum, specifically the caudate and putamen. Lesions of the mesostriatal pathway result in movement disorders, such as Parkinsonism, and are often treated with dopaminergic agonists.[177] The mesolimbic pathway serves the medial temporal cortex, amygdala, cingulate gyrus, and the nucleus accumbens. As such, lesions of this pathway may result in difficulty encoding and retrieving information (medial temporal cortex), information conflict resolution (cingulate gyrus), and "positive" symptoms of schizophrenia, such as hallucination. Dopaminergic antagonists are used to treat symptoms of schizophrenia. The mesocortical pathway arises largely from the ventral tegmental area and projects to the PFC. Lesions of this pathway may result in deficits of working memory, attention, abulia, hypokinesis, and the "negative" symptoms of schizophrenia.

Most of the serotonergic neurons (Figure 6.14) of the brain stem are located in the raphe nuclei. These neurons project to essentially the whole of the telencephalon. Some pathways project to the hypothalamus and are involved in cardiovascular function, and those projecting to the forebrain act to modulate the responsiveness of cortical neurons. Serotonergic neurons are involved in regulating attention and complex cognitive function.[180] Serotonin also impacts sexual function via a pathway from the raphe nucleus down the spinal cord, eating behaviors and appetite through a pathway to the hypothalamus, emotions (including anxiety and panic) and memory through a pathway to the limbic system, obsessive-compulsive disorder through a pathway to the basal ganglia, and cognition via a pathway to the PFC.

Cholinergic neurons (Figure 6.15) project from the mesopontine tegmentum and the basal forebrain. The neurons of the pontine region provide a descending projectional pathway to the nuclei of the pontine and medullary reticular formation. They also project in a major ascending pathway to the thalamus. The ascending pathway to the thalamus exerts an arousal effect that is mediated indirectly by excitatory projections from the thalamus to the cortex.[177] Projections arising in the basal forebrain provide indirect cholinergic input to the cortex. By contrast, cholinergic projections arising from the nucleus basalis neurons project entirely to nearly all the cerebral cortex. The hippocampal formation is fed by projections from the medial septal nuclei and the nucleus of the diagonal band of Broca. Cholinergic neurons of the descending pathway are thought to impact the sleep–wake cycle via these projections. Cholinergic blockade of central cholinergic transmission results in delirium, and blockade of the striatal neurons results in movement disorders.[177] The primary function of acetylcholine is found in attention, memory, and learning.

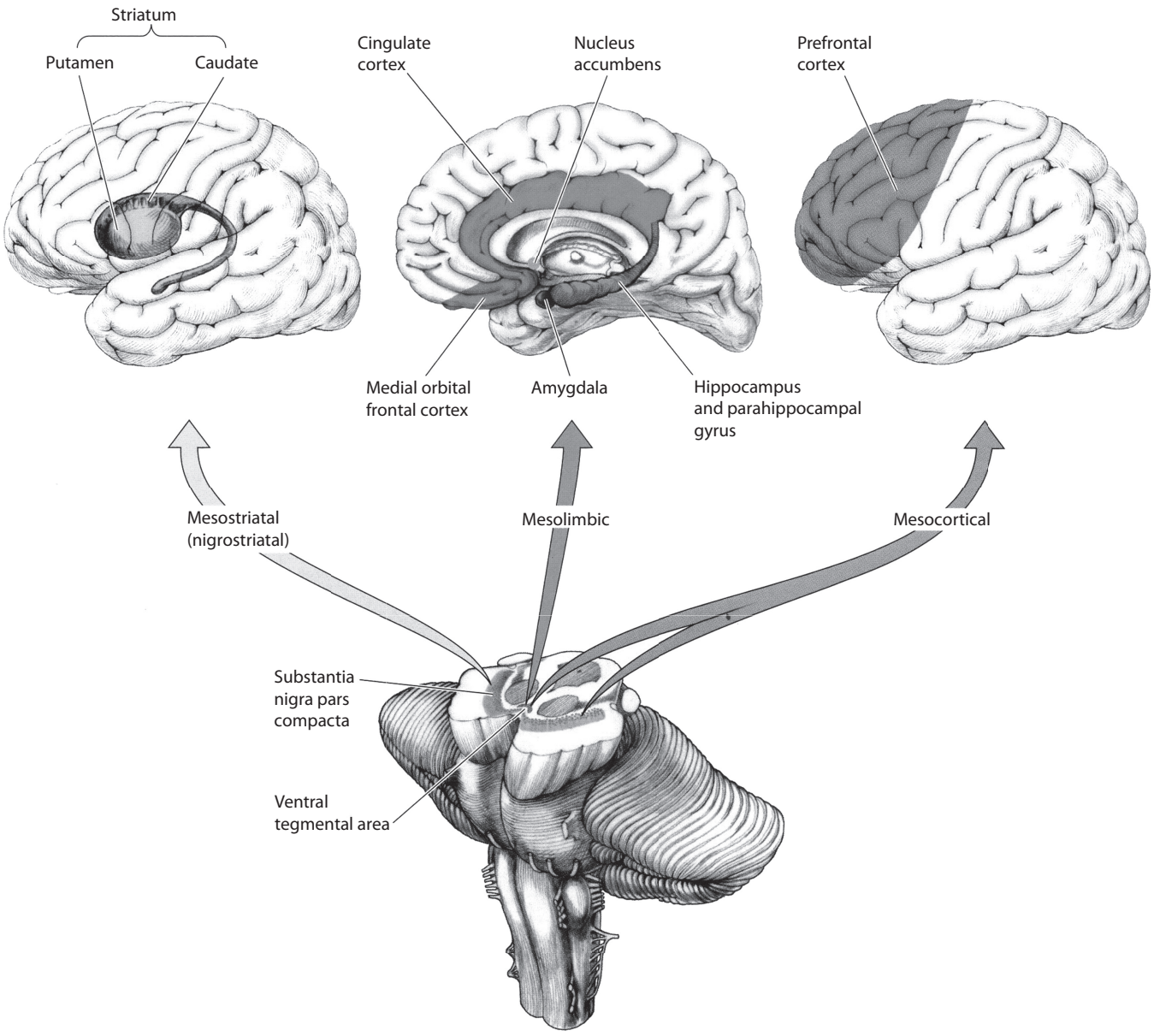


Figure 6.13 **(See color insert.)** Dopaminergic projection systems. (From Blumenfeld, H., *Neuroanatomy through Clinical Cases*, Sinauer Associates, Inc., Sunderland, MD, 2002, p. 595. With permission from Sinauer.)

Histaminergic neurons (Figure 6.16) are located in the posterior lateral hypothalamus and the tuberomammillary nucleus.[178] These neurons project to the spinal cord and to the entire cortex. These projections are thought to contribute to cortical arousal and to an arousal response at the level of the brain stem.

Once neurotransmitters are released into a synapse, they must be removed from the cleft via one of three mechanisms in order to preserve responsivity of the synapse. Neurotransmitters can be removed by diffusion, enzymatic degradation, and reuptake. Reuptake is the most common mechanism used for inactivation. Enzymatic degradation and reuptake offer two important means of pharmacological intervention in neurotransmission.

NETWORKS AND COGNITIVE FUNCTION

Specific functions

WORKING MEMORY

Working memory has been found to activate different networks depending upon the nature of the stimulus. Distinctions include storage of spatial, verbal, and object stimuli; whether working memory is continually updated; and the degree of executive processing or demand.[181]

Working memory has been conceived to consist of a number of independent subsystems, processes, and mechanisms.[182] These include a phonological loop (speech-based information), a visuospatial sketchpad (visual and spatial

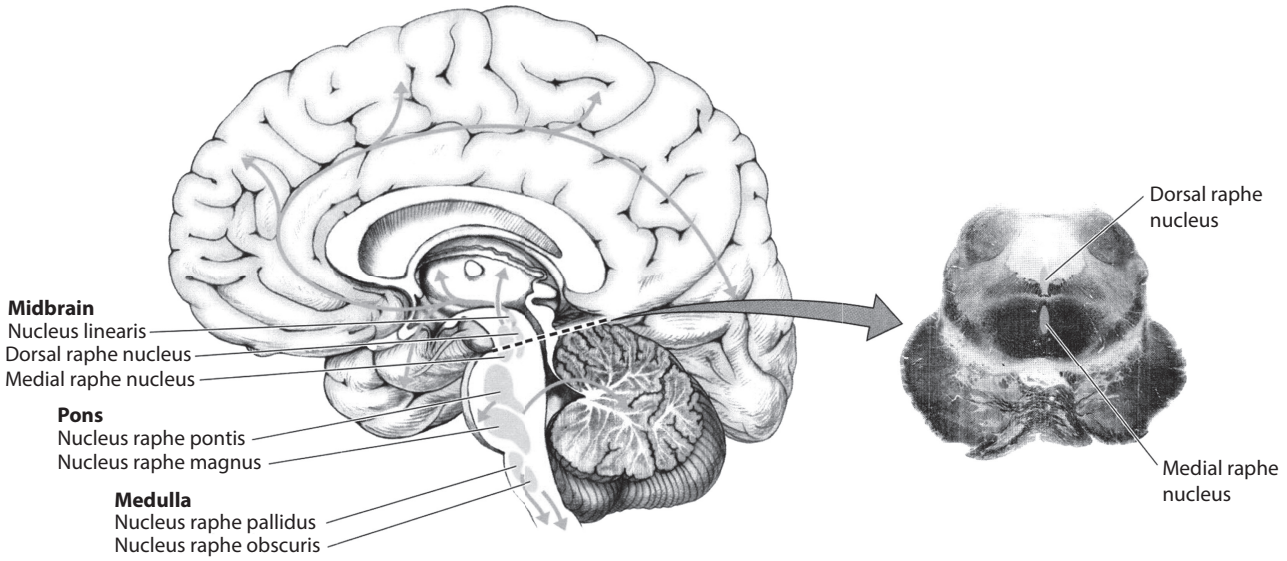


Figure 6.14 **(See color insert.)** Serotonergic projection systems. (Line drawing from Blumenfeld, H., *Neuroanatomy through Clinical Cases*, Sinauer Associates, Inc., Sunderland, MD, 2002, p. 597. Reprinted with permission from Sinauer. Photograph from Martin, J. H., *Neuroanatomy: Text and Atlas*, 2nd ed., Appleton & Lange, Stamford, CT, 1996, p. 522. Reprinted with permission from McGraw-Hill.)

information), a central executive (relating the content of working memory to long-term memory), and an episodic buffer (integrating information working memory and long-term memory components into coherent complex structures).

The PFC has been shown to reliably activate during working memory tasks and is critical in the maintenance and integration of verbal and spatial information.[183] PFC appears engaged in tasks involving both the central executive and the episodic buffer. Tasks that involve the episodic buffer activate the right PFC.[182] The phonological loop activates areas associated with linguistic processing. The visuospatial sketchpad activates the inferior and superior parietal cortices, which are implicated in integration of spatial cognition and visual information.[184]

A meta-analysis using the BrainMap database was conducted to determine the existence of overlap and gender-specific working memory networks.[184] Concordant working memory networks were shown to involve the bilateral middle frontal gyri, left cingulate gyrus, right precuneus, left inferior and superior parietal lobes, right claustrum, and the left middle temporal gyrus in both men and women. Females showed consistent activation of the anterior cingulate, bilateral amygdala, and right hippocampus of the limbic system and an extensive prefrontal network including bilateral middle frontal gyri. Males, however, demonstrated activation of the cerebellum, portions of the superior parietal lobe, the left insula, and bilateral thalamus.

DECISION-MAKING

Decision-making represents one of the most common and important aspects of higher executive function in man. As described in other chapters in this text on cognition, a number of processes contribute to the ability to conceive of problems and concoct their solutions. Similarly, those processes are widely distributed across neural structures and networks. Table 6.1 depicts specific neurologic structures and their respective impact on skills and abilities critical to decision making.

PERCEPTUAL DECISION-MAKING

An fMRI activation likelihood estimation meta-analysis was completed to review the role of frontoparietal network involvement in perceptual decision making.[185] Several distinct cortical areas were consistently implicated. They included the bilateral presupplementary motor area, bilateral anterior insula, right putamen, right opercular supramarginal area of the supramarginal gyrus, and the left middle frontal gyrus.

As difficulty increases, recruited areas include the right presupplementary motor area, bilateral anterior insula, bilateral precentral gyrus, bilateral inferior frontal gyri, and the left superior frontal gyrus. As reward influences decision making, areas recruited include frontal and subcortical areas, such as the bilateral striatum, right substantia nigra, right inferior frontal gyrus, left insula, and right superior medial gyrus.

PROSPECTIVE MEMORY

Clear differences are found in dorsal and ventral network activation for different phases of prospective memory.[186] Detailed discussion of the posited multiple phases of prospective memory is beyond the scope of this chapter (see McDaniel and Einstein[187]); however, support is found for involvement of the dorsal network in intention maintenance and for the ventral network in the retrieval phase of prospective memory.[186]

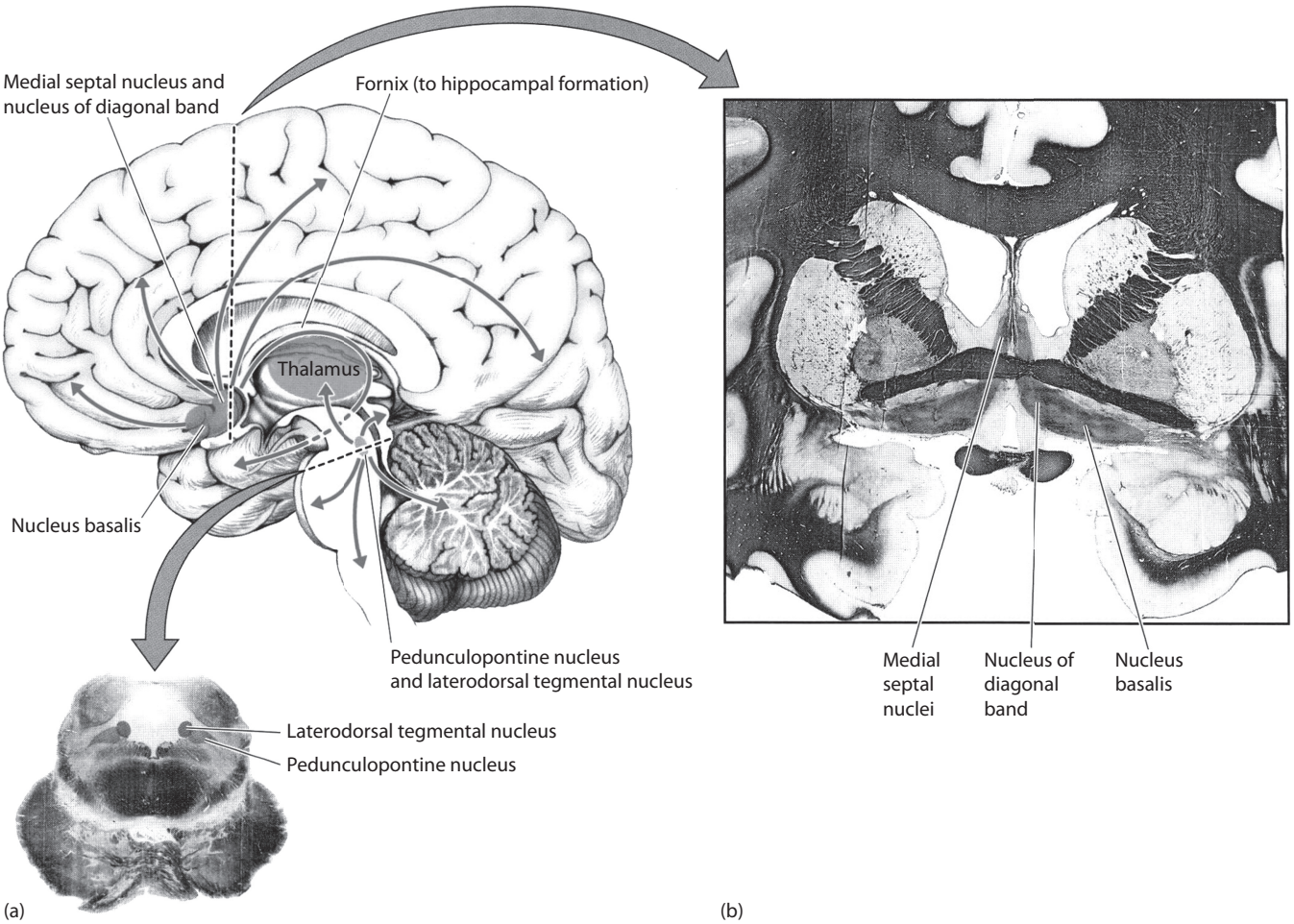


Figure 6.15 **(See color insert.)** Cholinergic projection systems. (a) Transverse view of the midbrain tegmentum; (b) coronal view of the medial septal nuclei, nucleus of diagonal band, and the nucleus basalis. (Line drawing from Blumenfeld, H., *Neuroanatomy through Clinical Cases*, Sinauer Associates, Inc., Sunderland, MD, 2002, p. 594. Reprinted with permission from Sinauer. Photograph from Martin, J. H., *Neuroanatomy: Text and Atlas*, 2nd ed., Appleton & Lange, Stamford, CT, 1996, pp. 522, 542. Reprinted with permission from McGraw-Hill.)

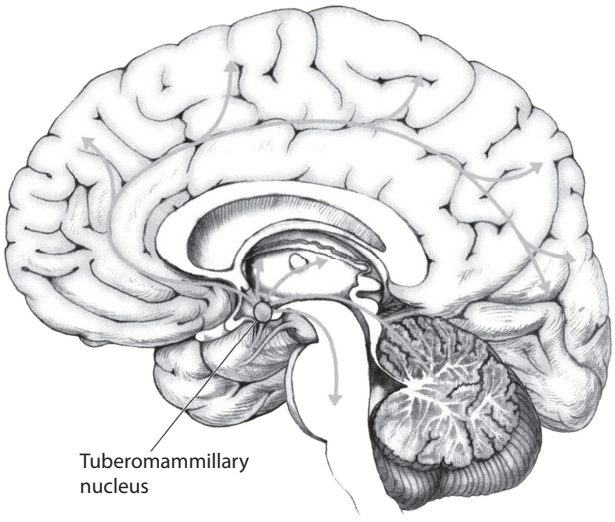


Figure 6.16 **(See color insert.)** Histaminergic projection systems. (From Blumenfeld, H., *Neuroanatomy through Clinical Cases*, Sinauer Associates, Inc., Sunderland, MD, 2002, p. 598. With permission from Sinauer.)

Default mode network

Three widely accepted primary networks, the default mode and dorsal and ventral networks, are differentially involved in episodic memory.[188] The default-mode network (DMN) consists of the anterior and posterior midline cortex, angular gyrus, and the medial temporal regions.

Based upon task-induced deactivation, anatomical connectivity, and diffusion MRI studies, the DMN is widely thought to consist of medial and lateral cortical and white matter structures.[189,190] The medial structures include a large portion of the medial PFC that extends dorsally and ventrally, medial parietal cortex comprised of the posterior cingulate cortex, and retrosplenial cortex. The precuneus cortex is implicated in some, but not all, default network regions.[191] The MTL is implicated, including the hippocampal formation and parahippocampal cortex, although less consistently. The lower prominence of this area may be linked to limitations of distortion and signal loss often associated with this region.

Table 6.1 Neurologic structures supporting skills and abilities critical to decision making

Function		Symptom
Orbitofrontal cortex	Incentive gain, emotional experiences associated with outcomes[192]	Disinhibition, impulsivity, increased risk-taking behavior, inability to alter behavior despite negative social consequences,[193] deficient counterfactual thinking, failure to regret,[194] failure to alter decisions despite negative outcome[193]
Anterior cingulate cortex	Complex decisions,[195,196] highly ambiguous decisions, recognizing and evaluating social cues,[197] performance optimization using previous learning[198]	Depression, difficulty linking decision-making to emotional tone[199,200]
Ventromedial prefrontal cortex		Increased risk taking,[201,202] failure to experience and recognize social meaningful stimuli,[203,204] low threshold for anger and frustration, impersonal approach toward moral decision making,[205] emotional bluntness toward risk[206]
Dorsolateral prefrontal cortex		Impairments in planning, inhibitory control, strategy development, cognitive flexibility, and working memory[207]
Frontostriatal connections	Goal-oriented behaviors[218,219]	Bradyphrenia, forgetfulness, apathy, depression[208,209]
Mediodorsal thalamic nucleus		Apathy, abulia, and disinhibition[210]
Posterior lobe of the cerebellum	Working memory, linguistic processing, visuospatial analysis, emotional regulation[211]	Deficits in executive function, linguistic processing, visuospatial function and affective dysregulation, disinhibition, loss of social boundaries, and impulsivity[212–214]

Laterally, the DMN includes the parietal region ventral to the intraparietal sulcus encompassing the posterior inferior parietal lobule and the angular gyrus.[190] The supramarginal gyrus, temporoparietal junction, and the lateral temporal lobe near the middle and inferior temporal gyri activate prominently. The lateral frontal lobe is also engaged in the inferior, middle and superior frontal gyri near Brodmann areas 47, 45, 8, 9, and 10.

Anatomical connectivity of the medial PFC shows connections to the posterior cingulate cortex, the superior temporal sulcus and anterior temporal pole, and the MTL.[215] The medial parietal cortex anatomical connectivity includes the posterior cingulate cortex, the retrosplenial cortex, and the precuneus.[215,216] The posterior cingulate cortex, in turn, is connected to many other default network regions. These include the medial PFC, inferior parietal lobule, lateral temporal lobe along the superior temporal sulcus, and the MTL, including the hippocampal formation and the parahippocampal cortex.[215,216]

The cingulum bundle connects the posterior cingulate cortex to the medial PFC and distinct white matter tracts connect the medial PFC to the inferior parietal lobe. The middle longitudinal fasciculus and cingulum connect the inferior parietal lobe to the lateral temporal lobe. Finally, the MTL connects to the posterior cingulate cortex and retrosplenial cortex.

DMN: Hubs and subsytems

The DMN appears to be organized into at least two hubs and two distinct subsystems that converge upon the hubs. The posterior cingulate cortex and the medial PFC seem to function as hubs. These hubs are served by a MTL subsystem, comprised of the hippocampal formation, parahippocampal cortex, retrosplenial cortex, ventral medial PFC, and posterior inferior parietal lobe. They are also served by a dorsal medial PFC subsystem comprised of the dorsal medial PFC, temporal parietal lobe, lateral temporal cortex, and temporal pole.

DMN functional significance

The DMN can be seen to functionally integrate memory, knowledge, and awareness of the self, social cognition, and emotion.

Response activation patterns provide support for the notion that the DMN engages in self-referential processing,[217] such as recollection memory and autobiographical memory.[218,219] Activation of the DMN is associated with encoding failure[220] and conceptual processing[221] and may represent the phenomena of the mind wandering[222] or internal distraction. Semantic knowledge retrieval activates many of the same regions as conceptual processing,

and perceptual tasks interrupt processes that activate many of these same regions.[221] The DMN is activated during prospection (imagining the future), mental navigation, and theory of mind activities wherein the individual considers the viewpoint of others.[219,223]

Two views of the DMN have been proposed. One suggests an external environmental monitoring role surveying for specific stimuli or significant unpredictable events, termed the "sentinel hypothesis." An alternate view suggests a larger role for internal mentation, specifically for spontaneous and goal-directed internal mentation. Lesser activation of the DMN is found as task difficulty increases. Easier and more practiced tasks are accompanied by more spontaneous thought. DMN activation occurs during episodic memory recall, and DMN activation inhibits episodic memory encoding.

The DMN can, perhaps, be considered the locus of large portions of knowledge of one's "self." DMN activation is seen for recollection of autobiographical information, evocation of self-knowing consciousness, subjective feeling of re-experiencing the past, recall of real versus imagined autobiographical events, simulated hypothetical personal events, realistic contexts of personal past experience, referencing personal information or reflection on personal preferences, personal moral dilemmas, beliefs, values, feelings, abilities, and physical attributes. The DMN activates in affect and motivation. The experience or anticipation of affect engages the DMN, including social threat, pain, and other aversive stimuli.

The DMN engages also as one extends oneself to consideration and realization of the states of others, such as when one considers information about similar or close others, including friends, family members, and romantic partners. The dorsal medial PFC subsystem activates when individuals reflect upon, evaluate, or appraise social information and extends to introspection of one's thoughts, feelings, and desires as well as those of others. Interpersonal social interactions activate this same system.

Frontoparietal attention networks

Two primary partially segregated networks have been identified that carry out distinct attentional functions: the dorsal and ventral frontoparietal networks.

The dorsal frontoparietal network regions include the dorsolateral PFC, the dorsal cingulate cortex/medial PFC, and dorsal posterior parietal cortex regions. The dorsal network is involved in know versus remember responses. The dorsal network engages in executive control processing, resolution of interference, and response selection.[181,224–226]

The ventral frontoparietal network includes the ventrolateral PFC, anterior insula, ventral posterior parietal cortex, and caudate nucleus. The ventral network shows increased activation with increasing salience and familiarity. Subjective salience drives this network and can be perceptual, emotional, or homeostatic. The ventral network activates when memories are strong, and salience for the retrieved information is high. This network serves to interrupt other processing, directing attention to salient events.[224]

The dorsal frontoparietal network resembles regions shown to mediate goal-directed, top-down attention processes,[224] and the ventral region resembles regions shown to mediate stimulus-driven bottom-up attention processes.[224]

SUMMARY

Injury to the body's most intricate and exquisite organ precipitates a combination of predictable and, as yet, unpredictable consequences that manifest in a wide variety of behavioral manifestations. The clinical reality is that most interventions today are geared toward reacting to the behavioral manifestations and applying treatments that remain largely focused on compensation for lost or altered function. The hope of this chapter is to provide the reader with information that may enable alternative approaches to brain injury that seek to take advantage of residual plasticity or enhance the plastic response of the brain as structures are encouraged to take on additional function. It has become increasingly necessary to better categorize types of injuries to the brain rather than lumping all injuries into just a few diagnostic distinctions, such as focal, multifocal, diffuse, penetrating, hemorrhagic, ischemic, or anoxic injury. Certainly, knowledge of the exact areas of the brain that have been injured should contribute to distinctions made in classification of injury and research pertaining to outcome differences that may be attributable to such distinctions. Rehabilitation after brain injury must develop such distinctions in order to distinguish those interventions that are preferential to various injuries and less so to others.

Cognitive recovery after brain injury occurs to varying degrees with ample evidence of improvements in areas such as attention, perception, learning, memory, planning, and problem solving. The clinical question should be focused on what can be done to further cognitive recovery of function, in keeping with recovery usually demonstrated in physical function. Discovery of methods of securing true recovery of cognitive function will best derive from knowledge of neurological anatomy and physiology associated with plasticity and targeted cognitive skill sets.

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7

TBI rehabilitation: Lessons learned from animal studies about mechanisms, timing, and combinatorial approaches

DOROTHY A. KOZLOWSKI

INTRODUCTION

In order for rehabilitation to be maximally effective following traumatic brain injury (TBI), it would be ideal to know exactly when the optimal time is for rehabilitation to start post-injury, how often and at what intensity it should be implemented, which strategies of rehabilitation work best together, and if there are any adjunctive therapies that should be added to traditional rehabilitation therapies that could enhance their effectiveness. Having the answers to these questions would greatly enhance the recovery of individuals with TBI. What may also be beneficial is a more complete understanding of the mechanisms by which rehabilitation works. Is rehabilitation strictly effective because of its ability to promote and enhance neuroplasticity, either directly or indirectly, or are the other physiological changes induced by rehabilitation more relevant to the promotion of recovery or perhaps a delicate balance between both? Would understanding such mechanisms allow us to develop better adjunctive therapies to enhance the effectiveness of traditional rehabilitation approaches?

These questions are not easy to answer but are being explored in more systematic ways.[1] Although there are studies that have attempted to answer some of these questions in clinical populations,[2,3] animal models have played a large role. The majority of these questions have primarily been addressed in animal models of stroke and applied to the rehabilitation of both stroke and TBI patients. Recently, however, my laboratory and others are beginning to explore these questions specifically in animal models of TBI. Doing so is demonstrating that the brain following TBI may be less responsive to rehabilitation and less plastic than the brain following stroke. This chapter discusses how examining rehabilitation, neuroplasticity, and adjunctive therapies in animal models of stroke and TBI can help inform studies to address these questions in clinical populations and improve rehabilitation of TBI patients in the clinic.

REHABILITATION PROMOTES RECOVERY OF FUNCTION AND PLASTICITY

The most influential demonstrations of the link between rehabilitation and neuroplasticity come from animal models of stroke and electrolytic lesions. The following sets of classic experiments demonstrated that plasticity occurs following stroke and focal lesions both around the injured area and in areas functionally connected to the injury. They also showed that this plasticity was linked to the behavior of the animal and important for behavioral recovery. Neuroplasticity can be measured experimentally in multiple ways. This chapter focuses primarily on structural plasticity (i.e., changes in dendritic arborization, synapse anatomy and number) and functional plasticity (i.e., changes in cortical maps that occur as a direct result of structural plasticity). These forms of plasticity have been linked to behavioral recovery and are thought to be a critical mechanism for neural rehabilitation. In turn, behavior and rehabilitation influence this plasticity.

Nudo, Kleim, and their colleagues have for many years been examining how the motor cortex reorganizes in primates and in rats.[4] Following a small infarct in the primary motor cortex (M1) of primates, they used intracortical microstimulation (ICMS) to map the brain to examine cortical map reorganization before and after a stroke. Using this technique, they found that, following an infarct, the hand representation in M1 shrinks significantly and that the surrounding elbow/shoulder areas take over what was once the hand area.[5,6] This plasticity was linked to the behavior of the monkey. The focal infarct resulted in significant deficits in manual dexterity in the hand and a resulting compensation using other body areas. The shrinking of the hand area in M1 could be spared, however, if these animals underwent rehabilitative training. The monkey rehabilitation consisted of wearing a jacket that encouraged the use of the impaired limb by restricting the use of the unimpaired limb and also receiving reach/grasp training daily of the impaired hand.[7] In addition to preventing the shrinking of the hand area, the rehabilitation also enhanced the functional recovery of the monkey post-stroke. Although the hand area shrinks immediately in M1, in the premotor cortex (PMv), the area thought to be responsible for planning movement, the area representing the hand increases post-infarct,[8,9] potentially to accommodate the extra planning needed to move the impaired hand properly. Kleim and colleagues have shown that these changes in motor maps occur in parallel with decreases and increases in synapse number in the areas being mapped.[10] Collectively, this work in the primate stroke model has demonstrated that areas surrounding infarcts reorganize post-stroke and that this reorganization can be altered by rehabilitation.

Plasticity can also occur in other areas of the brain following focal damage. Jones, Kozlowski, Schallert, and colleagues have demonstrated plasticity not just surrounding the injured cortex, but also in remote cortical areas, such as the homotopic cortex contralateral to injury. After unilateral electrolytic lesions of the forelimb sensorimotor cortex (FL-SMC; overlap of M1 and S1, see Figure 7.1), there is an increase in dendritic branching in the homotopic cortex (i.e., FL-SMC) contralateral to the injury. This increase peaks 14–18 days post-injury and, then, partially prunes back, reminiscent of cortical development.[11] The dendritic growth is followed by an increase in the number and efficacy of the synapses in the same region.[12] Similar effects have been found after unilateral ischemic lesions of the FL-SMC.[13] These changes in the contralateral homotopic cortex are directly linked to the behavior of the animal. Following a unilateral injury or stroke, the function of the limb contralateral to the injury is impaired, and both rats and humans rely on their unimpaired limb to perform their everyday skills.[14,15] Therefore, the plasticity in the homotopic cortex may be driven by the increased compensatory use of the unimpaired forelimb. Preventing rats from using their unimpaired forelimb (using limb restricting vests or casts) for the first 15 days post-lesion eliminates the neural plasticity seen in the contralateral FL-SMC[16] and results in a worsening of behavioral function,[17] suggesting that this neuroplasticity is behaviorally driven and may be important to behavioral recovery. Plasticity also involves a pruning back of dendrites and synapses following enhanced growth in the cortex contralateral to the unilateral injury as seen in development. Initially, it was thought that the pruning occurred due to the recovery of bilateral forelimb use. Interestingly, the pruning process is not significantly driven by behavior because forcing the use of the impaired limb during the pruning phase (days 15–30 post-lesion) does not affect the pruning process nor significantly affect behavioral recovery.[18] However, the pruning process is sensitive to pharmacological manipulation. When n-methyl-d-aspartate (NMDA) antagonists (such as MK801 or ETOH) are administered prior to the beginning of the pruning process, they prevent pruning and reinstate behavioral deficits.[19,20] These findings suggest that different phases of post-injury neural plasticity are differentially influenced, i.e., some by behavior, some pharmacologically.

Since these early findings, many studies have shown the behavioral benefits of using rehabilitative strategies such as motor skill learning,[14,21,22] forelimb constraint,[23] exercise,[24] and enriched environments[25] following animal models of focal lesions and stroke. It is beyond the scope of this chapter to review them all; however, these rehabilitative strategies have been shown to increase neuroplasticity and enhance behavioral function resulting in changes to rehabilitation strategies in clinical populations. Nevertheless, not all plasticity is good plasticity. It is known that, in addiction, for example, neural plasticity can actually be the underlying cause of cravings, withdrawal, and drug seeking/relapse.[26] Although the use of the uninjured forelimb after injury drives neuroplasticity in the contralateral cortex, it is well known that the reliance on the unimpaired limb can contribute to persistent dysfunction, i.e., "learned nonuse" of the impaired limb.[27] Jones and colleagues examined the role that the uninjured forelimb plays in both recovery and plasticity following stroke and found that training the uninjured forelimb after stroke can inhibit behavioral recovery of the impaired limb and limit the effect of rehabilitative training.[13,14,28] This was directly linked to a decreased responsiveness of the cortex surrounding the injury[28] and to decreased representations of the forelimb and aberrant synaptogenesis around the injured cortex.[29] These findings suggest that compensating with the uninjured forelimb or a rehabilitative strategy that includes training the unimpaired limb can result in aberrant plasticity that can impair behavioral recovery.

REHABILITATION AND PLASTICITY FOLLOWING TBI

Although there is extensive literature on structural neuroplasticity and rehabilitation in animal models of stroke, studies are lacking that examine this in similar ways post-TBI.[1,30,31] In animal models of TBI, such as the controlled cortical impact (CCI), fluid percussion injury (FPI), and

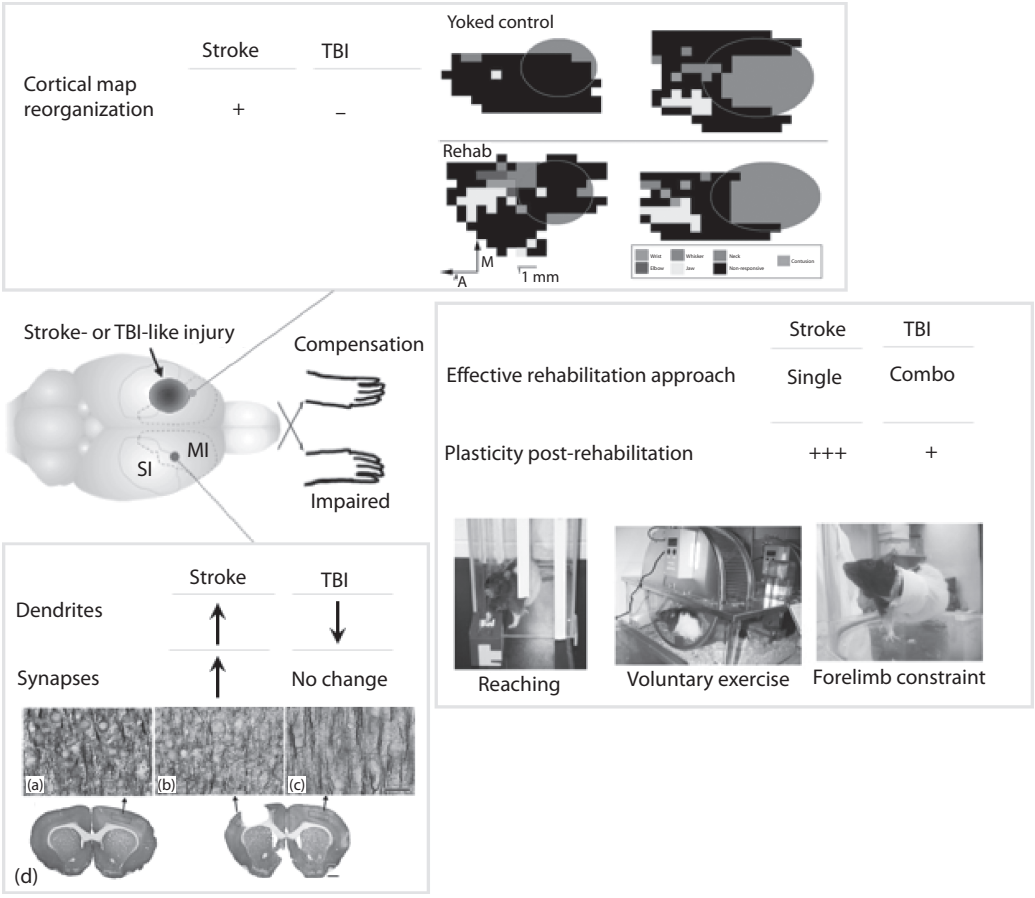

Figure 7.1 **(See color insert.)** Differences in neuroplasticity and rehabilitation in unilateral stroke vs. TBI to the FL-SMC. Unlike what is seen following stroke, TBI results in a lack of cortical reorganization (top box; as measured with intracortical microsimulation) and diminished structural plasticity (bottom box)—seen as a decrease in dendritic plasticity in the contralateral homotopic cortex (as measured with MAP immunostaining in uninjured cortex with robust staining [a] vs. decreased staining surrounding the injury [b] and in the contralateral homotopic cortex [c]). Compared to stroke, rats with TBI require a combination of three different types of rehabilitation approaches (reaching, exercise, and forelimb constraint—middle box) as opposed to just reaching alone, and this rehabilitation results in a minor amount of cortical reorganization (top box). (Modified from Kozlowski, D. A. and Jones, T. A. Plasticity and Recovery of the Injured Brain. In: Morganti-Kossman, C., Raghupathi, R. and Maas, A., eds., *Traumatic Brain and Spinal Cord Injury: Challenges and Developments in Research: Translating Research into Clinical Practice*. Cambridge University Press, 2012.)

weight drop models, plasticity has primarily been examined via expression of neurotrophic factors and inhibitors of neuroplasticity or other molecular markers of synaptic plasticity.[32] Collectively, these studies have primarily demonstrated decreased plasticity in the hippocampus[33–35] and cortex[36,37] and increased expression of plasticity inhibitors, such as chondroitin sulfate proteoglycans (CSPG).[38] Only a few studies have examined structural plasticity in the cortex following TBI, showing pericontusional axon sprouting following a CCI to the FL-SMC[38] and sprouting in the corticospinal tract following traditional parietal CCI (for review see Kozlowski and Jones[39]).[40,41]

Studies examining structural plasticity in the cortex in the same manner as in the stroke models described above, however, have not been conducted in TBI until recently. Our lab, in collaboration with Jones and Adkins, has recently begun to examine whether the cortical structural plasticity found in stroke models discussed above also occurs following CCI. The general assumption has been that the cortical plasticity seen following stroke also occurs following TBI without direct empirical evidence. Using a CCI of the FL-SMC, we demonstrated behavioral asymmetries in forelimb use and a reliance on the unimpaired forelimb similar to what was seen following electrolytic or ischemic lesions along with a comparable area of tissue loss. Despite these similarities, there were no increases in dendritic arborization. In fact, dendritic arborization decreased bilaterally post-CCI (see Figure 7.1).[42] The number of synapses was only increased in the injured hemisphere at approximately 2 weeks post-CCI, but this increase returned to pre-injury levels within a month. No changes in synaptic density were seen in the contralateral cortex. These drastic differences in plasticity responses in the contralateral homotopic cortex (compared to the enhanced compensatory response seen

following ischemia) could not be attributed to neuronal degeneration in the contralateral cortex (as measured by FluoroJade®) nor to enhanced expression of the myelin-associated growth inhibitor Nogo-A, which was increased in the injured cortex but not in the contralateral cortex.[42] Using ICMS, we also showed that there was a significant lack of responsiveness and minimal cortical reorganization surrounding the contusion cavity as opposed to the extensive cortical reorganization seen surrounding the infarct (see Figure 7.1).[43] This is consistent with Nudo et al., who also showed that CCI fails to result in the spontaneous reorganization typical of focal stroke.[44] Although the premotor hand area in the monkey increases its size following ischemic injury to M1, in rats with M1 CCI, the size of the (roughly homologous) rostral forelimb representation area decreased in size by approximately 60%. Although more studies are needed to understand these differences between CCI and ischemic injury effects on neuroplasticity, these findings suggest that the behaviorally driven compensatory neuroplasticity seen following electrolytic lesions and stroke may not occur in animal models of TBI.

The limited degree of plasticity evident following CCI suggests that rehabilitation techniques effective in animal models of stroke described in the previous section may not be as effective after TBI. We, therefore, examined whether three different types of rehabilitation strategies, previously demonstrated to be effective alone or in combination following an animal model of focal ischemia, would enhance recovery in an animal model of TBI (CCI centered over the FL-SMC). Rats with CCI received reach training (daily starting 3 days post-TBI); reach training and exercise (running wheel exposure for 6 hours daily starting 14 days post-TBI until the end of the study); or reach training, exercise, and forelimb constraint (constraint of the unimpaired forelimb using a vest that prevented the use of the limb for weight bearing movements and manipulation from days 10–20 post-CCI; see Figure 7.1). Measures of motor and sensorimotor function were examined until 42 days post-injury. The results indicated that deficits in skilled reaching, motor coordination, and the coordinated use of forelimbs for weight bearing exploration were only minimized when rats received a combination of all three rehabilitative therapies.[45] Behavioral recovery was not significantly affected by reach training alone, contrary to the findings in stroke where reach training alone was beneficial. Constraint alone was only beneficial in the promotion of more symmetrical limb use following TBI. Combining these three rehabilitation tasks also enlarged the area of wrist representation in the motor cortex, suggesting that some rehabilitation could induce some cortical reorganization following TBI (see Figure 7.1)[43] but not to the extent seen by rehabilitation following focal ischemic lesions. Together, these findings suggest that neural plasticity may be limited following TBI and, therefore, the rehabilitation protocol required to produce behavioral enhancements may need to be more extensive and require more combinations than that seen in a similarly sized lesion due to stroke. We are currently exploring the underlying mechanisms of why combined rehabilitation approaches in TBI are needed, compared to a single approach following stroke. Although rehabilitation therapists working in TBI rehabilitation have confirmed these findings anecdotally, future clinical studies comparing rehabilitation approaches for stroke versus TBI are very important for confirming this data in patient populations.

REHABILITATION TIMING

The brain following injury has been described as a "fertile milieu" for structural changes such as dendritic growth and pruning.[46] This neuroplasticity appears to be transient, however, and limited to an acute post-injury period similar to the anatomical critical periods seen in development.[47,48] If rehabilitation relies on the potential for neuroplasticity post-injury, then the critical window for therapeutic effectiveness is also limited. The question, "When is the optimal time to initiate neural rehabilitation?" is one that still has not been answered, especially following TBI.[3,49] Nevertheless, most would agree that rehabilitation is more effective when started earlier as opposed to later post-injury. Reach training following an ischemic infarct in the rat that starts 4 days post-stroke enhances recovery, while the same training started at 25 days post-stroke is ineffective.[50] Similarly, in monkeys, reach training that begins within 1 week post-infarct but not 30 days post-infarct can spare hand representation in the motor cortex.[51,52] In stroke patients, those who receive constraint-induced movement therapy (CIMT) starting between 3 and 9 months post-stroke fare better than those with whom CIMT is started after 9 months.[53] In TBI patients, meta-analysis and retrospective studies show that outcomes were better if patients received rehabilitation within the first year[31] or early (while in acute care) following TBI.[49] Although all of these studies point to the idea that earlier is better, the definition of early differs, and there is no definitive guideline that points to a particular time point post-injury during which rehabilitation is maximally effective. In addition, animal models demonstrate that different rehabilitation strategies seem to have different time points during which they are maximally effective, suggesting that the optimal rehabilitation time point may differ depending on the rehabilitation strategy.

Although starting rehabilitation early seems to be beneficial, it has also been demonstrated that care needs to be taken to not initiate rehabilitation too early. Following a focal electrolytic lesion to the FL-SMC, rats were prevented from using their nonimpaired forelimb to examine its effect on neural plasticity in the contralateral homotopic cortex.[16] This manipulation resulted in the forced use of the impaired limb, similar to CIMT, for the first 14 days post-injury (the time frame during which the increase in plasticity was seen to occur). Forcing the use of the impaired limb during this time point did not result in a rehabilitative effect. On the contrary, it resulted in an exaggeration of the injury and in significant motor deficits that did not recover over time.[17]

This type of exaggeration of injury following forced use of the impaired forelimb was also seen following ischemic injury[54] and in animal models of TBI, such as the CCI and FPI.[55] Following an FPI, forcing the use of the impaired limb creates contusions that correspond structurally to an area of increased glucose metabolism,[56] suggesting that an overactivation of metabolism may play a role in the exaggeration of injury. Other possible mechanisms include hyperthermia or increased glutamate because forced use of the forelimb was shown to increase brain temperature,[57] and blocking glutamate transmission via MK801 during forced use spared neural tissue.[58] Humm narrowed down the window of susceptibility to the first 7 days post-injury.[59] The exaggeration of injury occurs when the unimpaired limb is immobilized during the first 7 days post-lesion but not if the limb is immobilized during days 8–15 post-injury, suggesting that acute constraint-induced therapy may be harmful following neural injury. Although later immobilization in the rat (days 8–15) post-lesion did not exaggerate the injury, it still interfered with recovery of sensorimotor function, suggesting that there are time windows not only for neuroanatomical effects of rehabilitation, but also for behavioral effects of rehabilitation.[59]

It is difficult to translate a vulnerable period in the rat to a vulnerable period in a patient with stroke or TBI. Nevertheless, in a phase II clinical trial (VECTORS study) that examined CIMT in stroke patients receiving acute inpatient stroke rehabilitation, it was demonstrated that patients who received high intensity CIMT starting 9 ± 4 days post-stroke for 2 weeks showed significantly less improvement in arm function at day 90.[60] This suggests that early, intense rehabilitation in humans may also not be optimal with at least the first week post-stroke as a vulnerable period. The vulnerable period following TBI is unknown.

Early, intense overuse of an impaired extremity can disrupt the natural course of neural and functional recovery, but what about underuse? To investigate this question, the impaired forelimb was restrained beginning immediately after FL-SMC injury[61] and lasting for 1 week. This forced nonuse of the impaired limb was followed either by cast removal or forced *overuse* of the impaired forelimb (casting of the nonimpaired forelimb). Rats that had the cast removed after 1 week of forced nonuse of the impaired limb continued to rely on the less-affected (ipsilateral) forelimb. In rats that were then switched to forced overuse of the impaired forelimb, exaggeration of injury was seen as described above. Note that it had previously been shown that forced overuse of the impaired forelimb during the second post-injury week did not cause exaggeration of injury. Thus, forcing nonuse during the first week extended the window of vulnerability to use-dependent exaggeration of injury. These results have important clinical implications because brain trauma can result in hemi-neglect and/or reduced motor function, in which case an impaired extremity may remain underused for an extended period of time. Subsequent vigorous physical rehabilitative efforts in such cases may be ill-advised.

Careful examination of vulnerable periods for rehabilitation in animal models of TBI has not been extensively explored. Voluntary exercise for 2 weeks immediately following a FPI has been shown to impede recovery and minimize the expression of growth factors, but if the exercise post-TBI is delayed for 2 weeks, it enhances plasticity and behavioral recovery.[62,63] This time window also depends on the severity of the injury. Griesbach and colleagues examined whether the severity of injury may be an important factor determining the effectiveness of exercise post-TBI. Rats with mild FPI showed an exercise-induced increase in neurotrophic factor expression in the hippocampus but only when exposed from days 14–20 post-injury. Rats with moderate injuries only showed increases when the exercise was conducted during days 30–36 post-injury. Thus, increased severity of injury may have shifted the therapeutic time window.

The question, "When is the appropriate and optimal time to begin rehabilitation?" is still not answered. Although earlier rehabilitation is generally understood to be optimal, rehabilitation that is too early may be deleterious. In addition, the severity of injury and the rehabilitation therapeutic approach as well as individual differences in the deficits and mobility of the patient post-TBI can move this therapeutic window. Further systematic research in both animal models and clinical populations is needed to fine-tune therapeutic windows.

COMBINING REHABILITATION WITH ADJUNCTIVE THERAPIES: WHAT'S THE WINNING COMBINATION?

TBI inpatient rehabilitation is naturally designed to include multiple different rehabilitation therapies and approaches, including physical, occupational, speech, and cognitive therapies along with management of nutrition and psychotherapy. These therapies are designed to address the individual deficits and dysfunction of each patient and are designed to provide an individualized therapeutic program for each patient. In animal models of TBI, rehabilitation is usually examined using one type of approach, i.e., exercise, enriched environment, or CIMT. In our lab, we used the CCI model of TBI in the rat and examined three different sensorimotor rehabilitation tasks, i.e., skilled reaching, exercise, and forelimb constraint. We showed that the combination of the three different motor rehabilitation tasks was necessary to show any type of benefit to sensorimotor function[44] as opposed to just one or two tasks. This combination of rehabilitative approaches was able to induce cortical reorganization in an otherwise fairly unresponsive cortex post-injury.[42] The other most-studied model of rehabilitation following TBI in rodents is the enriched environment: a large cage filled with many rodents that provide a social environment in which rodents are exposed to a variety of stimuli that enhance sensory systems and encourage climbing and motor maneuvering as well as sensory and motor skills in addition to physical exercise. Rats placed in enriched

environments post-TBI show enhanced recovery of both cognitive and sensorimotor skills and increased expression of markers of neuroplasticity, such as growth factors, and have less cell death and degeneration compared to injured rats housed in standard group housing (for review see Bondi et al.[64]). These effects are also sensitive to timing of administration and sex of the animal.[65,66] Together these studies support the multidisciplinary and combinatorial approach to rehabilitation suggesting that TBI patients may need a combination of therapeutic approaches to address a behavioral deficit as opposed to just one (which may be beneficial post-stroke). However, what is less understood is, within each of these therapeutic approaches, which combination of tasks is optimal to promote full recovery. Additionally, what is it about each task that lends itself to being beneficial? These are not easy questions to answer and, ultimately in a clinical setting, may vary from individual to individual. Nevertheless, more research is necessary in both animal models and human patient populations to understand the underlying mechanisms by which individual rehabilitation approaches and combinations promote recovery. Doing so may help outline which combinations are most effective and why.

In addition to multiple rehabilitation therapies, patients are also typically administered medications post-TBI. Some of these medications may be beneficial and enhance the benefits of therapy, and others may impede its progress. Research examining the effects of combining rehabilitation with pharmacological manipulations following TBI is beginning to emerge. For example, combining physical rehabilitation or an enriched environment with drugs such as anti-inflammatory agents,[67] serotonin agonists,[68] and amphetamine[69] produced mixed results with anti-inflammatory agents enhancing the effects of rehabilitation, amphetamine having no additive effect at all, and serotonin agonists enhancing some, but not all, of the benefits of rehabilitation. In stroke and spinal cord injury models combining rehabilitation paradigms with antidepressants, neurotrophic factors, and agents against plasticity inhibitors, such as anti-Nogo-A, result, for the most part, in an additive benefit.[3] However, studies to the contrary exist. Therefore, the combination of rehabilitation with one specific class of pharmacological agents is not yet warranted. Future studies are necessary that focus on exploring the interactions between rehabilitation and pharmaceuticals most often delivered to patients with TBI with an eye toward those in which underlying mechanisms might be elucidated and complementary.

The use of cortical stimulation as a potential therapeutic is being explored for multiple neural diseases and injury states as well as to enhance cognition in aging individuals.[70–73] Stimulation applied directly to the epidural or subdural space along with transcranial cortical stimulation is being examined alone and in combination with rehabilitative paradigms. In rats with ischemic lesions, motor skills training combined with electrical stimulation of the motor cortex during rehabilitation starting 10 days post-infarct significantly improved reaching ability (some to preoperative levels) and increased dendritic arborization around the infarct.[74,75] However, these effects can differ due to injury severity with more severely injured rats showing less benefit.[76] Additionally, these effects are timing-dependent with benefits seen primarily when stimulation and rehabilitation are paired within the first 2 weeks post-infarct, but not if they are delayed 3 months.[77]

Cortical stimulation for TBI was initially considered a dangerous option due to the risk of increased seizures following TBI. However, clinical trials of brain stimulation for multiple disorders has minimized this concern by showing that stimulation produced only a few documented seizures.[73] Therefore, studies are beginning to explore stimulation alone and in combination with rehabilitation post-TBI. Cortical stimulation alone following a weight drop model of TBI enhanced motor functioning and brain activity.[78,79] In a model of pediatric TBI, transcranial magnetic stimulation increased brain activity and expression of cellular markers of neuroplasticity as well as decreased hyperactivity in behavioral tests.[80] Cortical stimulation is also being combined with rehabilitation following TBI. In a rodent model of CCI to the FL-SMC, combining three different types of rehabilitation along with epidural stimulation of the motor cortex significantly enhanced behavioral function and increased wrist representation in the motor cortex.[81] In a pilot clinical trial, repeated anodal transcranial direct current stimulation combined with cognitive rehabilitation in severe TBI patients showed larger effect sizes on measures of attention and memory; however, they were not significantly different from controls.[82] Future research is necessary to determine the appropriate type of cortical stimulation along with stimulation intensity parameters and location following TBI. Combining this optimal stimulation paradigm with rehabilitation strategies post-TBI may prove to provide additive benefit.

CONCLUSIONS AND FUTURE DIRECTIONS

The use of animal models of stroke and TBI to examine the phenomena of neural plasticity and recovery of function and how these are influenced by rehabilitation is essential to the furthering of rehabilitation programs for individuals with TBI and other neurological disorders. Animal studies have 1) demonstrated the link between neural plasticity and neurorehabilitation; 2) shown that there are sensitive periods for the effectiveness of rehabilitation; 3) suggested that although behavioral symptoms may be similar following stroke and TBI, the brain's response and readiness for rehabilitation may differ in different injury states and diseases; and 4) shown that rehabilitation can be enhanced by pairing it with pharmaceuticals or stimulation therapy. Although the questions posted in the introduction have not been conclusively addressed, animal studies have helped provide guidelines and questions for clinical practice. In addition to continuing to address these questions in animal

models of TBI specifically, future studies are needed to explore whether a biomarker might be available that could help determine an individual's readiness for rehabilitation or a marker to demonstrate if a rehabilitative approach is effectively enhancing neuroplasticity or another known physiological mechanism of rehabilitation. Because rehabilitation is the only current method of treatment available for individuals with TBI, it is crucial to continue to examine its efficacy in controlled clinical trials and to assess whether findings in animal models can be translated to the clinic.

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8

Diet and exercise interventions to promote metabolic homeostasis in TBI pathology

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INTRODUCTION

An increasing number of studies indicate that environmental conditions and experiences encountered in the daily life of individuals can dramatically impact the capacity of the brain to resist challenges associated with injury, toxicity, or disease. In particular, abundant evidence indicates that diet and exercise are two noninvasive approaches that can be used to enhance the function of the brain.[1] Diet and exercise management have become a realistic possibility that can be easily implemented to reduce the burden of traumatic brain injury (TBI). This chapter discusses current advances in the understanding of the molecular mechanisms by which diet and exercise influence brain function and plasticity during homestatic conditions and after TBI.

According to the results of epidemiological studies, there is a clear association between diet and mental health,[2–8] and a growing body of literature provides mechanistic support for the influence of diet on the brain. Bioactive components of foods affect brain function, particularly influencing cell energy metabolism with subsequent effects on inflammatory events, oxidative stress, and synaptic plasticity.[9] Certain foods, such as polyunsaturated fatty acids, have a characteristic beneficial action for the brain by providing structural support to neurons, acting as free radical scavengers, protecting the brain against oxidative stress, and reducing inflammatory processes. Other foods, such as sugars and saturated fatty acids, tip homeostasis toward a more inflammatory environment that can become harmful in the long term. In turn, exercise, by using similar mechanisms to healthy foods, can promote brain plasticity and function, and its action has been shown to be instrumental for reducing the decline of mental function associated with aging[10] and to facilitate functional recovery after neurological injury or disease.[11]

The pathobiology of TBI is characterized by a phase of metabolic dysfunction in which neurons cannot comply with energy demands; thereby, neuronal vitality and functionality are compromised as well as the possibility to recover functionality. TBI patients sustaining even moderate injury experience sudden abnormalities in the control of brain metabolism,[12–17] which may increase the risk for secondary brain injury.[18–20] The prospect of TBI is becoming even more alarming in the surge of metabolic neuropathies associated with the consumption of high caloric foods, particularly those enriched in fructose.[21] Indeed, according to recent reports, more than 40% of the U.S. population are diabetic or prediabetic.[22] One of the most

intriguing aspects of TBI is that patients become vulnerable to a large range of psychiatric disorders, such as depression and anxiety-like behavior, under minimal neuronal death.[23] A failure in energy balance is gaining recognition as a factor in the pathogenesis of a large number of neurological disorders.[24–27] The fact that loss of metabolic homeostasis is intrinsically involved in the pathobiology of TBI[28] suggests that a reduction of metabolic function by consumption of unhealthy diets can likely worsen the outcome of TBI patients.[29,30] A growing line of research indicates that approaches leading to promoting energy homeostasis are a productive strategy to support brain function[31] and to counteract the pathogenesis of TBI.[32]

LIFESTYLE AND MENTAL HEALTH

Abundant evidence in humans supports the effects of diet and exercise on maintaining normal brain function and reducing the incidence of neurodegenerative disorders. For example, a systematic meta-analysis revealed an inverse association between depression and a Mediterranean-style diet high in fruits, vegetables, fish, and whole grains.[3,6–8] In turn, consumption of a Western-style diet high in snack foods and sugars has been found to be associated with the incidence of psychiatric-like disorders, such as anxiety and depression.[3,8] According to animal studies, sustained consumption of saturated fat and sugar impairs learning and memory[33–36] and increases anxiety-like behavior[35,37] and depression.[38] In turn, it is becoming well accepted that consumption of omega-3 fatty acids, such as DHA and EPA,[39–49] and vegetable-based extracts high in polyphenolic and flavonoid components[50–57] improve brain function, cognition, and emotional health. Therefore, careful management of dietary ingredients is a suitable strategy to regulate long-term cognitive and emotional health.

THE METABOLIC PATHOLOGY OF TBI

TBI compromises mitochondrial bioenergetics[58,59] as well as a wide range of molecular systems important for energy homeostasis, which suggests that the TBI brain is vulnerable to metabolic disorders. Several of the molecular systems closely linked to cell metabolic regulation also play important actions in the maintenance of neuronal plasticity. In particular, TBI reduces levels of the peroxisome proliferator-activated receptor gamma coactivator-1alpha (PGC-1α), which is a transcriptional regulator of various transcription factors important for maintenance of mitochondrial homeostasis.[60] PGC-1α activates various transcription factors crucial for mitochondrial function, including nuclear respiratory factors (NRFs). In turn, NRFs activate the mitochondrial transcription factor A (TFAM) that regulates mitochondrial DNA (mtDNA) transcription and replication.[61,62] The action of PGC-1α seems also operational for maintaining behavioral performance as these experiments have shown that latency time in the Barnes maze changes in proportion to changes in PGC-1α. The interaction between cell metabolism and neuronal plasticity is exemplified by findings that PGC-1α can also influence brain-derived neurotrophic factor (BDNF).[63] Levels of BDNF are reduced after TBI, which can compromise brain plasticity and function as BDNF supports a range of metabolic events important for neuronal function.[64,65] Treatment with the BDNF agonist 7,8-DHF has been shown to restore levels of PGC-1α and TFAM and mitigate TBI pathology.

BDNF: A LINK BETWEEN METABOLIC AND COGNITIVE DYSFUNCTIONS IN THE PATHOLOGY OF TBI

BDNF is one of the most influential molecules for maintaining brain function and plasticity. BDNF has the capacity to protect neurons against a variety of neurological insults and to counteract psychiatric-like disorders[66] within the spectrum of TBI pathology. New evidence suggests a therapeutic role of BDNF for ameliorating cognition and mood (depression, anxiety, bipolar) disorders.[66] According to our research, the powerful action of BDNF on supporting neuronal plasticity and behavior stems from its unique capacity to work at the interface between metabolism and synaptic plasticity.[67] Indeed, BDNF is emerging as an important modulator of mitochondrial bioenergetics[65] and the capacity of neurons to metabolize glucose.[64] These newly discovered BDNF actions are in addition to the well-known role of BDNF as a regulator of the survival, growth, and differentiation of neurons during development.[68,69] In the adult central nervous system (CNS), BDNF is able to modulate the efficacy of neurotransmitter release,[70] to stimulate the synthesis of synaptic proteins,[71,72] and to regulate transcriptional factors;[73,74] all of these actions are important for behavioral regulation. In the hippocampus, BDNF is capable of inducing a rapid potentiation of glutamate-mediated synaptic transmission[75] and long-term potentiation (LTP).[76] LTP, considered an electrophysiological correlate of learning and memory,[77] selectively increases BDNF mRNA levels in the hippocampus. Genetic deletion of the BDNF gene[78] or functional blocking of BDNF[79,80] have been demonstrated to impair learning and memory in rats. Replenishing the depleted hippocampus with exogenous BDNF seems to ameliorate these deficits.[81] In addition, exogenous BDNF application[82] or transfection of hippocampal slices with a BDNF-expressing adenovirus[83] has been shown to restore the ability to induce LTP.

The signaling of BDNF through its TrkB receptor is critically important for cell functioning such that dysfunction of TrkB is known to be a factor in various neurodegenerative diseases and psychiatric disorders.[84] The capacity of BDNF-TrkB signaling to engage metabolism and plasticity makes it a susceptible target for a wide variety of metabolic interventions that can be instrumental to mitigate the pathology associated with TBI. In particular, BDNF and subsequent cognitive performance have been shown to be susceptible to several types of dietary manipulations. For example, consumption of a diet high in saturated fats and sugar[33,34] reduces BDNF levels and adult neurogenesis in

the hippocampus[85] and impairs hippocampus-dependent learning and memory.[86,87] A failure in cognitive function caused by high-sugar/high-fat diets is accompanied by oxidative stress,[87,88] inflammation,[87] or impaired blood–brain barrier integrity.[86] In turn, omega-3 fatty acids have been shown to elevate the expression of BDNF.[89] As discussed subsequently, one of the strongest behavioral interventions to boost BDNF levels and learning and memory is exercise. For example, it is well known that hippocampal BDNF is increased with exercise[90–92] and that exercise reduces cognitive deficits and attenuates hippocampal BDNF reductions caused by consumption of a high-fat/high-sugar diet.[34,36]

The extraordinary capacity of BDNF to support several aspects of brain plasticity and function is negated by the poor pharmacokinetic profile of BDNF. Agents that stimulate the TrkB receptor could be ideal therapeutic agents to combat the TBI pathology without the poor pharmacokinetics of BDNF. This is a desired goal because BDNF and TrkB signaling are reduced in the TBI pathology,[93] thereby reducing neuronal function and making neurons more vulnerable to secondary challenges. The 7,8-dihydroxyflavone (7,8-DHF) is a member of the flavonoid family of compounds present in fruits and vegetables, which can mimic BDNF signaling through the TrkB receptor.[94] Furthermore, the facts that 7,8-DHF crosses the blood–brain barrier and has a safe pharmacokinetic profile make 7,8-DHF an excellent therapeutic agent.[94,95] The binding of 7,8-DHF to the cysteine cluster 2 and leucine-rich region in the extracellular domain of the TrkB receptor provokes TrkB receptor dimerization and autophosphorylation, which leads to activation of downstream signaling cascades similar to BDNF. In particular, 7,8-DHF has demonstrated neuroprotective effects against oxidative stress incurred from glutamate toxicity,[96] decreases infarct volumes in stroke, and reduces toxicity in an animal model of Parkinson's disease.[94] These features portray 7,8-DHF as an ideal candidate to be used therapeutically to counteract the effects of the TBI pathology. Systemic administration of 7,8-DHF using an animal model of TBI has been shown to significantly attenuate disrupted memory function by activating hippocampal TrkB receptor.[97] In addition, the 7,8-DHF treatment was effective in ameliorating the effects of TBI on CREB phosphorylation, GAP-43, and syntaxin-3 levels. The action of 7,8-DHF engaged molecular systems important for energy homeostasis (AMPK and SIRT1) and mitochondrial biogenesis (PGC-1α, TFAM, and COII), indicating that activation of cellular energy metabolism may be an important step for the action of 7,8-DHF on plasticity. Information gathered so far portrays the potential of 7,8-DHF as an efficacious and noninvasive therapeutic agent to downgrade the TBI pathology.

ROLE OF NUTRITIONAL FACTORS IN NORMAL BRAIN HEALTH AND AFTER TBI

Omega-3 fatty acids

Docosahexaenoic acid (DHA, C22: 6n-30) is the most prevalent omega 3 (n-3) fatty acid in brain tissue. Structurally, DHA truly stands as brain food as it accounts for roughly one third of the fatty acids present in the gray matter of the brain and is essential to normal healthy brain development.[98–102] DHA deficiency has been linked to several neurocognitive disorders, such as anxiety-like behavior,[103,104] Alzheimer's disease (AD),[105] major depressive disorder,[45] schizophrenia[106] with psychosis,[107] and impaired attention.[108,109] Notably, DHA supplementation has been shown to relieve anxiety.[110–113] The action of DHA is particularly important during growth and development,[98–102,104,114–117] and during challenging situations, such as aging[118–121] or brain injury.[122,123] Evidence suggests that DHA serves to improve neuronal function by supporting synaptic membrane fluidity and function and regulating gene expression and cell signaling.[124] Because the human body is not efficient in producing its own DHA, supplementation of diet with foods rich in DHA is important in insuring proper function of neurons and in facilitating neuronal recovery after injury.[89] Omega-3 fatty acids also reduce oxidative stress damage.[89,125] Even more interesting, DHA dietary supplementation along with exercise has been shown to have additive effects on synaptic plasticity and cognition in rodents under normal conditions.[126]

The sysnthesis of omega-3 fatty acids requires n-3 fatty acid precursors for *de novo* synthesis in mammals, and the efficiency of the body to synthesize n–3 fatty acids is poor. A primary source of DHA is fish, or it can be synthesized from plant-derived n-3 fatty acid precursors. Vegetable sources of the precursor for DHA—α-linolenic acid (C18:3 n-3; ALA)—include sunflower and soybean oil (>50% of the fat).[127] DHA synthesis from its precursors ALA, eicosapentaenoic acid EPA (C20:5n-3), and docosapentaenoic acid (C22:5n-3; DPA) mainly takes place in the liver because the synthesis of DHA in the brain is very limited.[128] In general, the conversion efficiency of DHA synthesis from ALA is quite low.[129–131] Vegetarians and vegans thus have reduced plasma DHA compared to omnivores,[132–135] yet many populations thrive on an entirely plant-based diet and are able to obtain adequate levels of DHA to support cognitive development and plasticity. This raises the question as to whether other food components commonly consumed in traditional vegetarian diets could enhance DHA content in the brain and the synthesis of DHA from plant-based sources. As discussed subsequently, the polyphenol turmeric has been shown to aid in the synthesis of DHA in the body from endogenous precursors.

PLASMA MEMBRANE IS SUSCEPTIBLE TO THE EFFECTS OF TBI AND DIET

The integrity and function of plasma membranes is a crucial topic in the TBI field as membranes are very fragile to lipid peroxidation. Dietary deficiency of n-3 fatty acids during brain formation has detrimental effects on cognitive abilities,[115,116,136–138] but cognitive performance can be improved by increasing brain DHA content.[138] Animal studies strongly suggest that reduced content of DHA in

plasma membranes increases the risk for neurocognitive disorders.[139,140] Omega-3 polyunsaturated fatty acids (PUFA) significantly increase the unsaturation index and fluidity of membranes, and monounsaturated and saturated fatty acids do the opposite.[141] Higher saturated fatty acid intake is associated with worse global cognitive and verbal memory trajectories.[142] Saturated fat intake is associated with impaired memory in middle-aged people[143] and in women with type 2 diabetes[144] and is associated with age-related cognitive decline and mild cognitive impairment.[145] Additionally, over a 6-year period, a diet high in saturated fat was associated with declining cognitive test scores.[146] Although saturated fatty acids have gained a bad reputation based on results of several studies in which cognition has been assessed, their final connotation in brain function is still controversial as they contribute substrate, such as cholesterol for synthesis of myelin. It noteworthy that the health benefits of polyunsaturated fatty acids are negated when these fats are oxidized because lipid peroxides are detrimental to cellular functions. As discussed subsequently, curcumin prevents reduced DHA content in the brain following brain trauma, benefiting brain plasticity as well as reducing oxidative damage.[122]

THE ANTIOXIDANT ACTION OF VITAMIN E ON TBI

Vitamin E and its main form, gamma-tocopherol, are abundant in certain oils, such as soybean and corn, and have shown promise in protecting neurons against degeneration and oxidative damage in an animal model of TBI.[147,148] Vitamin E functions as an antioxidant, reducing free radicals in the brain that would otherwise impede optimal function of neurons. Vitamin E has shown positive effects on memory performance in older people,[149] indicating its ability to maintain neuronal health. A different study in aging mice revealed the benefits of vitamin E by showing a correlation between the amount of ingested vitamin E and improved neurological performance, survival, and brain mitochondrial function.[150]

DIETARY POLYPHENOLS AND COGNITIVE PERFORMANCE: CURCUMINOIDS

Polyphenols are a large group of chemical substances found in plants characterized by the presence of multiple phenol groups. The Indian curry spice turmeric (*Curcuma Longa*) contains the polyphenolic secondary metabolite curcumin, which is a staple in Indian cooking. As an antioxidant, anti-inflammatory, and anti-amyloidal agent, curcumin can improve cognitive function in patients with AD. For example, assessment of cognitive function in a population of elderly Asians with a mental examination test revealed that those who consumed curry very frequently performed significantly better in comparison to those who almost never or rarely consumed curry,[151] suggesting a strong capacity for curcumin to affect brain function. Interestingly, the frequent use of turmeric in India is one of the main explanations for the low percentage of clinical cases with AD in India.[152] Additionally, the supplementation of curcumin into the diets for 3 weeks before[153] or after[154] experimental TBI using the fluid percussion injury model lessened the consequences of the injury on synaptic plasticity markers and cognitive function tasks. Curcumin has been reported to cross the blood–brain barrier.[155,156] Ironically, DHA is poorly consumed in India based on the vegetarian prevalence in the population.

In addition to having profound antioxidant[153] and anti-inflammatory effects,[41] we recently showed that curcumin prevents a reduction of DHA content in the brain following brain trauma, benefiting brain plasticity as well as reducing oxidative damage.[122] It is known that DHA is an essential component of nerve cell membranes,[157,158] but the synthesis of DHA is very limited in the brain.[128] Although DHA can be obtained through animal sources in the diet, vegetarians and vegans may face challenges getting adequate dietary DHA.[134] Increasingly, vegetarianism and veganism is being adopted in the Western world.[159] Circulating omega 3 fatty acids are lower in vegetarians and non–fish eaters than in people who consume fish.[160] Elevations in brain DHA were closely associated with reduced anxiety-like behavior. These results are in agreement with previous studies describing an association between DHA dietary deficiency and anxiety-like behavior.[104] Sources of DHA for the brain include dietary sources, such as fish, and DHA synthesized by the liver from precursors, such as ALA (C18:3n-3), DPA (C22:5n-3), EPA (C20:5n-3), and tetracosahexaenoic acid (C24:6n-3).[161–164] The combined supplementation with curcumin + DHA reduced brain content of the DHA precursor n-3 DPA, raising the question as to whether curcumin stimulates the synthesis of DHA.[122] Curcumin elevates levels of DHA in the brain, and these effects required the presence of ALA in the diet. Although the rate of synthesis is low, the brain seems to have the capacity to synthesize DHA from ALA.[128] Curcumin elevates DHA synthesis from n-3 precursors in liver cells, and that, in combination with dietary ALA, increases DHA content in vivo in both the liver and brain. These data strongly suggest that curcumin increases the hepatic synthesis of DHA from its precursors. Thus, it is possible that curcumin elevates DHA in the brain, in part, through *de novo* synthesis in brain tissue. This possibility warrants further investigation although liver synthesis seems the more likely contributor to increased brain pools of DHA because curcumin is highly metabolized in the liver.[165] Because the liver is the primary site for most of the DHA synthesis in the body, this raises the question as to whether some of the health effects of curcumin can be attributed to the synthesis of DHA. These findings have important implications for human health and the prevention of cognitive disease, particularly for populations eating a plant-based diet or who do not consume fish, a primary source of DHA, because DHA is essential for brain function, and its deficiency is implicated in many types of neurological disorders.

DIETARY POLYPHENOLS AND COGNITIVE PERFORMANCE: RESVERATROL

Resveratrol is a nonflavonoid polyphenolic found in grapes, red wine, and berries. There are two isomeric forms of resveratrol, the biologically inactive *cis*-resveratrol and the most biologically active *trans*resveratrol (*trans*-3,4,5-trihydroxystilbene). Resveratrol has shown good efficacy in reducing several pathological events in TBI.[166–168] This compound has been the focus of a number of studies demonstrating its antioxidant, anti-inflammatory, antimutagenic, and anticarcinogenic effects.[169–171] Interestingly, several epidemiological studies indicate an inverse correlation of wine consumption and incidence of AD.[172–174] It is well known that reducing food intake or caloric restriction extends lifespan in a wide range of species. It has been found that resveratrol can mimic dietary restriction and trigger sirtuin proteins.[175] The sirtuin enzymes are a phylogenetically conserved family of enzymes that catalyze NAD-dependent protein deacetylation. In yeast, sir2 is essential for lifespan extension by caloric restriction and a variety of other stresses, including increased temperature, amino acid restriction, and osmotic shock.[176,177]

DIETARY FLAVONOIDS AND COGNITIVE FUNCTION

Flavonoids are found in various fruits and vegetables or their subproducts, such as berries (e.g., blueberries, strawberries), tea, and red wine. Flavonoids have positive effects on cognition for the treatment of various brain diseases including brain injury,[178] and age-related cognitive decay in rodents.[179] The mechanisms by which flavonoids exert their actions in neural repair are diverse, such as promoting neuronal signaling and increasing production of antioxidant and anti-inflammatory agents. Dietary flavonoids have been shown to promote activation of growth factor signaling pathways and enhance spatial memory.[50] Berries, such as blueberries[180,181] and strawberries,[53] are particularly rich in flavonoids. In humans, a higher intake of these berries is associated with slower cognitive decline,[53] which was validated in rodents in studies showing that supplementation with strawberry and blueberry extracts attenuates cognitive deficits and supports synaptic plasticity.[182,183] Green tea contains potent dietary flavonoids, and long-term exposure to green tea reverses some of the degenerative effects of aging in the hippocampus of rats.[184] Green tea is rich in flavonoids (30% of dry weight of a leaf)[185] with the main compounds being epigallocatechin gallate (EGCG), (-)-epigallocatechin (EGC), (-)-epicatechin (EC), and (-)-epicatechin-3-gallate (ECG). EGCG has been shown to attenuate mitochondrial dysfunction in culture[186] and to protect against the effects of oxidative injury involving the BDNF system.[187] Catechin intake has been associated with a wide variety of beneficial health effects.[188] Daily doses of the green tea catechins have been shown to prevent memory loss and DNA oxidative damage[189] and to enhance or prevent the age-related decline of spatial memory in rodents.[190,191] The prevention of cerebrovascular diseases or stroke by green tea has been evidenced during a 4-year follow-up study with 5,910 individuals. The incidence of cerebral hemorrhage and stroke were twofold higher in those who consumed less than five cups than in those who consumed five cups or more daily.[192] An inverse correlation between black tea consumption and the incidence of stroke was also replicated in a cohort of 552 men aged 50–69 years and followed up for 15 years.[193] Although there is no significant outcome relative to tea consumption in AD case control, there are several in vitro studies showing that green tea extract may protect neurons from Aβ-induced damages.[194–197]

As discussed previously, 7,8-DHF is a derivative of flavones that acts as a small molecule TrkB receptor agonist.[94] 7,8-DHF readily crosses the blood–brain barrier and remains active for an extended time relative to BDNF, making it a good therapeutic agent for disorders within the scope of BDNF treatment.[198,199] We have recently shown that 7,8-DHF rescues impaired cognitive performance caused by TBI by activating the TrkB receptor.[97] Other naturally occurring flavonoids may act via BDNF signaling pathways, such as the citrus flavonoid heptamethoxyflavone, which elevates BDNF and increases the number of differentiating neuronal precursor cells.[200]

METABOLIC DISTURBANCES AS A SIGNATURE OF TBI PATHOLOGY

Although certain foods can enhance brain function and plasticity, sustained consumption of saturated fats and sugar can do the opposite. Molteni and colleagues originally showed that rats fed a diet high in saturated fats and refined sugars (similar in composition to "junk food") for a period of 1–2 months reduced performance on the spatial learning maze test.[201] Elevated levels of oxidative stress were among the effects of this diet, which can be reversed by antioxidant treatment[202] or exercise.[34] These findings are alarming based on the reported rise in consumption of high caloric foods that has triggered a metabolic epidemic such that the number of diabetic and prediabetic persons in the United States is estimated at more than 40% of the population.[22] Accordingly, we have recently reported the impact of fructose consumption on the capacity of the brain to cope with the pathology of TBI. Indeed, a high-fructose diet has been shown to induce several physiological parameters of metabolic disease, such as reduced sensitivity to insulin and increased risk factors for cardiometabolic disease in humans and rodent.[203] Overconsumption of dietary fructose for a duration sufficient to disrupt peripheral metabolism exacerbates cognitive dysfunction caused by TBI and reduces levels of proteins related to brain plasticity and cell energy metabolism. An increasing body of evidence indicates that diet-induced metabolic disease poses a threat for brain function and can increase the risk for neurological and psychiatric disorders.[204] Our current data set provides the framework for a potential mechanism by which dietary

fructose may disturb cognition during TBI by disrupting oxidative metabolism, thereby interfering with the activation of systems that support synaptic plasticity. In addition, animals on a high fructose diet or animals with TBI both had reduced markers of cell energy metabolism (PGC-1α, TFAM, and SIRT1) and markers of neuronal plasticity (synaptophysin, GAP43, BDNF-TrkB signaling) as well as elevated markers of lipid peroxidation (4HNE). These molecular systems are at the critical interface between cell metabolism and synaptic plasticity, thereby having a strong impact on cognitive function. These data piece together to reveal the compelling possibility that metabolic perturbation elicited by diet is a predictor of cognitive impairment due to injury. Indeed, a new line of studies in humans indicates an association between metabolic disease and disturbances in cognition, emotional health, and reduced quality of life.[205]

The effects of fructose and TBI appeared to impact the actions of key elements in the BDNF signaling cascade. Disruption in BDNF function has been implicated in the pathophysiology of several neuropsychological disorders, such as depression[206] and schizophrenia.[207] Both BDNF/trkB[208] and insulin receptor[209] pathways have been reported to act via PI3K/Akt/mTOR signaling, which is an essential pathway for synaptic plasticity and cognition. As an indicator of changes in synaptic plasticity, we observed changes in levels of synaptophysin, a marker of synaptic growth, and the growth-associated protein 43 (GAP-43), which is expressed at high levels during neuronal growth and is associated with axonal sprouting.[210,211] Our results showed that fructose and TBI each, individually, reduced the levels of synaptophysin and that fructose potentiated the reduction caused by TBI. Taken together, these data strongly suggest that fructose exacerbates the effects of TBI on neuronal growth and synaptic plasticity.

Reduced sensitivity to the action of insulin is considered a predictor of poor clinical outcome in TBI patients.[30] The action of insulin has been associated with mitochondrial function regulation,[212,213] which suggests that insulin can influence a range of cellular processes. Our current data show that fructose reduces insulin receptor signaling in the hippocampus and potentiates the effects of TBI on behavioral dysfunction and plasticity. The insulin receptor has a role in cognitive function such that reduced activity of this receptor in the hippocampus impairs LTP consistent with poor recognition memory.[214] Similarly, our data show that the detrimental effects of fructose on hippocampal insulin receptor signaling were commensurable to poor performance in the Barnes maze. Mitochondrial abnormalities are getting recognition as a common feature for neurological disorders.[27] A failure in mitochondrial function is as a major sequel of TBI[215] and suggests that metabolic disorders can exacerbate the pathobiology of TBI. We observed reduced mitochondrial function in both fructose and TBI conditions as evidenced by a decreased mitochondrial respiratory capacity linked with ATP turnover.

DIET AND EPIGENETICS: A PLATFORM FOR EXTENDING ACTION AND INFLUENCING NEUROLOGICAL DISORDERS

The results of new and exciting epidemiological studies suggest that dietary factors have the capacity to influence the risk for metabolic diseases, such as diabetes, and this can be transmitted across generations.[216] It is coming to be understood that the pathobiology of several psychiatric disorders, such as depression, resides in epigenetic modifications of the genome.[217,218] The original concept of epigenetics implies the idea that modifications in DNA expression and function can contribute to inheritance of information.[219] Some of these ideas have received partial support, such as the negative impact of early stress on behavioral responses across generations and on the regulation of DNA methylation in the germ line.[220] Epigenetic modifications include chromatin remodeling, histone tail modifications, DNA methylation, and noncoding RNA and microRNA gene regulation.[221] Evidence is starting to reveal that various epigenetic modifications are inheritable[222] and that dietary factors can affect epigenetic mechanisms at multiple levels.[222] In particular, DNA methylation and histone acetylation are particularly susceptible to the effects of environmental manipulations and affect cognitive function and emotions. For example, chronic administration of a diet rich in saturated fats and sugar has been shown to increase DNA methylation of the opioid receptor in the context of reward-related behavior.[223] Unlike genetic mutations, epigenetic marks are potentially reversible, such that nutritional supplementation and/or pharmaceutical therapies may be developed for prevention and treatment of neurological disorders.

An exercise regimen known for its capacity to enhance learning and memory has been shown to promote remodeling of chromatin containing the BDNF gene in conjunction with elevation of levels of p-Ca^{2+}/calmodulin-dependent protein kinases II (CaMKII) and p-cAMP response element-binding protein (CREB) molecules intimately involved in the pathways by which neural activity engages mechanisms of epigenetic regulation to stimulate BDNF transcription.[224] The results of these studies emphasize the influence of metabolic signals on the epigenome and their capacity to alter feeding behavior. Even more recently, it has been shown that the effects of a DHA diet can be saved as changes in DNA methylation for the BDNF gene that could provide long-term protection to metabolic insults.[225] Several lines of information appear to indicate that the BDNF gene is a major target of epigenetic modifications associated with environmental pressure, such as early-life adversity,[226] and environmental enrichment.[227]

EFFECT OF EXERCISE ON BRAIN HEALTH AND REPAIR

Given that most of our current genome remains unchanged from the times of our ancestors,[228] who had to perform

abundant exercise for survival, the prevalence of inactivity in U.S. society is abnormal. The lack of physical activity and unhealthy eating are major factors for the prevalence of obesity in modern industrialized societies[229,230] and derived metabolic dysfunctions, such as type 2 diabetes.[229,231,232] A sedentary lifestyle or the lack of physical activity seems to be the primary causal factor responsible for about one third of deaths due to coronary heart disease, colon, cancer, and type 2 diabetes.[233] Exercise enhances learning and memory under a variety of conditions (see Gomez-Pinilla and Hillman for review[234]) such that, in humans, it can attenuate the mental decline associated with aging[235] and enhance the mental capacity of juveniles.[236] Exercise, similar to diet, activates multiple hippocampal proteins associated with energy metabolism and synaptic plasticity,[237] such as BDNF[238,239] and insulin-like growth factor-1 (IGF-1). Blocking the action of BDNF during voluntary exercise decreases the effects of exercise on energy metabolic molecules, such as adenosine monophosphate-activated protein kinase (AMPK), suggesting that cellular energy metabolism interacts with BDNF-mediated plasticity.[239] Exercise has the capacity to enhance learning and memory[240–242] under a variety of conditions, from counteracting the mental decline that comes with age[10] to facilitating functional recovery after brain injury and disease.[11,243,244] Much like a healthy diet, physical activity is thought to benefit neuronal function. Exercise has been found to play an important role in the regulation of neurite development[245] maintenance of the synaptic structure,[246] axonal elongation,[34] neurogenesis in the adult brain,[242] and after brain and spinal cord injuries. Exercise has been shown to benefit in animal models of Parkinson's disease.[247] Exercise has also been shown to facilitate functional recovery. When physical therapy was implemented to treat Parkinson's disease, patients showed signs of increased motor ability.[248] Exercise applied after experimental TBI has also been shown to have beneficial effects, but these effects seem to depend on the postinjury resting period and the severity of the injury.[249]

COLLABORATIVE EFFECTS OF DIET AND EXERCISE

Feeding and exercise comprise part of the spectrum through which the environment has been instrumental in shaping the modern brain over thousands of years of evolution. Experimental studies in rodents have shown that exercise works in complementation with a DHA-rich diet to influence molecular systems underlying cognitive function.[250] A possible mechanism for this complementary action of exercise is exerted via restoring membrane homeostasis after TBI, which is necessary for supporting synaptic plasticity and cognition.[251] The combined effects of a flavonoid-enriched diet and exercise potentiate the elevation of genes that are generally benevolent for neuronal plasticity and health while decreasing genes involved with deleterious processes, such as inflammation and cell death.[252] Exercise has also proven to be effective in reducing the effects of unhealthy diets, i.e., counteracting the decline in hippocampal BDNF-mediated synaptic plasticity and in spatial learning skills of rats exposed to saturated fats.[34]

CONCLUSION

Lifestyle conditions, such as diet and exercise, can contribute to the ability of the brain to counteract neurological disorders. Specific diets and exercise routines have been shown to impact select factors that can make the brain more resistant to damage, to facilitate synaptic transmission, and to improve cognitive abilities. Managed dietary manipulations and exercise have strong therapeutic potential, and this capacity could be implemented to improve the outcome of TBI. Cumulative information indicates that diet and exercise activate systems concerned with whole body metabolism and brain plasticity. Because TBI is devastatingly difficult to treat, mainly due to the multifactorial aspect of its pathology[253] compromising the ability of the brain to metabolize energy.[254,255] TBI patients experience sudden abnormalities in the control of brain glucose metabolism,[14,15] which can increase the risk of secondary brain damage.[19,20] Overload of an already disrupted brain metabolic regulation[256] through consumption of high caloric foods or sedentary lifestyle can make the TBI pathology even worse[29] and can increase incidence of long-term neurological and psychiatric disorders.[257] The magnitude of the problem is even bigger considering that the incidence of TBI and associated cognitive disorders are on the rise[258] as is the prevalence of metabolic disease.[259] Therefore, the information discussed here can be used as a platform to promote healthy lifestyle and to use the power of diet and exercise to design rehabilitative programs to increase the outcome of TBI patients.

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9

Disruptions in physical substrates of vision following traumatic brain injury

RICHARD E. HELVIE

INTRODUCTION

It is impossible to formulate a meaningful mental model of how traumatic brain injury (TBI) can disrupt the physical substrates of vision without having detailed knowledge of the visual system. The visual system is one of the most complex and well studied in the brain. Handling the majority of incoming sensory inputs, it is highly developed with myriad connections and interconnections to other networks of motor, sensory, and the cognitive domains. Much of the beginning of this chapter is dedicated to discussing general brain anatomy and subsequent modular organization and connectivity.

Advances in neuroimaging and electroencephalography have allowed for a more delineated study of vision including computerized tomography (CT) for tissue density and magnetic resonance imaging (MRI) for different tissue properties; functional (brain activation) imaging includes positron emission tomography (PET) and single photon emission tomography (SPECT), both using radioisotope tracers in blood and tissue; functional MRI, using deoxyhemoglobin levels in blood; magnetoencephalography (MEG), recording magnetic fields induced by neural discharges; magnetic resonance spectroscopy (MRS), recording metabolic concentration in tissue; and tomographic electroencephalography (EEG), recording summed neuronal discharges.

VISION

Vision is one of the most amazing miracles of life. It is estimated that 70% of the sensory input of the brain is vision and more than 50% of the brain is involved in visual processing; More than 32 visual areas have been located in

the cortex.[1] It is a journey of light rays being transformed into visual cognition. It is an emergent process, requiring continuous evaluation of spatial maps, creating an internal representation of the external world, which allows us to integrate and navigate through our environment. It not only informs us of where our bodies are in space but what is in space and the relationship of objects to each other. We have to stretch our imagination to conceptualize how a small, distorted, upside-down visual representation received in our retina can come to represent the rich environment we perceive. Visual perception results when the visual system transforms the two-dimensional patterns of light received at the retina into a coherent representation of a three-dimensional world. Light rays, derived from the physical properties of objects and surfaces, are received in the retina, and the spatial and temporal patterns of that light are processed both through parallel and serial systems in a hierarchical fashion to produce our internal representations. Objects are recognized and categorized by the physical attributes of form, color, motion, and location in space. These include both moving and stationary objects, written language, music, mathematics, and faces.

Once processed, visual information is integrated with other sensory modalities, such as touch and sound. This information is involved in the prediction, preparation, and control of motor movements needed for activities of daily living. Additional integration occurs as visual output is projected to distributed neural networks to higher cortical areas involved with memory, language, and emotion.

The goal of this chapter is to present a systematic approach to this complex process that can serve as a guide in understanding vision, allowing proper diagnosis and appropriate treatment for visual deficits.

GENERAL ANATOMY

Core components

The brain has two solid components and four anatomical parts. The two core components are the gray matter and the white matter. Gray matter can be likened to a series of computers with the white matter being the wiring connecting them to one another. The major component of the gray matter includes neuronal cell bodies, called neurons. They have cellular extensions called dendrites and axons (the latter both myelinated and unmyelinated). Neurons are electrically polarized cells that specialize for conductance of electrical impulses projected down the axons and transmitted chemically over spaces called synapses to the dendrites of the next neuron. Electrical connectivity of large groups of neurons is termed brain circuitry. Besides intercellular connectivity, there is also intracellular connectivity, referred to as transduction. This total transfer of information is called cell signaling.

The brain has one hundred billion neurons. Neurons are located not only in the cortex, but also in subcortical structures called nuclei. There are two types of neurons in the cortex, principal neurons (which consist of 80% of the neuron population and are glutamatergic) and interneurons (comprising the other 20%, which are GABAergic).[2] Glutaminergic neurons are excitatory, and GABAergic neurons are inhibitory. All brain behavior is dependent upon cell signaling over brain circuitry.

There are two types of brain cells, neurons and neuroglial cells. The major types of neuroglial cells in the gray matter are astrocytes, oligodendrocytes, and microglial cells. Astrocytes form the building blocks of the blood-brain barrier, help to create an extracellular space to clean toxins and waste products, remove excessive neurotransmitters from synapse, refuel the brain at night to provide energy and secrete neurotropic factors. Astrocytes' main role is to maintain neuronal function. Oligodendrocytes produce myelin to insulate axons, produce all brain cholesterol, and have a very high metabolic rate, replicating themselves throughout life. Microglial cells are the resident macrophages of the central nervous system, protecting the brain through neuroinflammatory responses. The obvious difference between neurons and neuroglial cells is the latter do not have axons or dendrites or produce action potentials.

White matter is the other component of the brain. It consists predominately of large bundles of myelinated axons and the same neuroglial cells present in the gray matter, i.e., astrocytes, oligodendrocytes, and microglial. Axons are bundled together in the white matter and interconnect cortical and subcortical areas and the cerebral hemispheres. They are bidirectional in transmission capabilities. They are described in different terms, including fasciculus, tract, bundle, lemniscus, and funiculus.

The pattern of development varies significantly between the gray and white matter. Nearly the entire complement of brain neurons is formed before birth with development beginning early in gestation.[3] Gray matter remains relatively constant in volume throughout adult life; however, contrary to earlier opinion, neurogenesis does occur throughout life. White matter formation does not begin until the third trimester of gestation and is only partially complete at birth. Even at 2 years of age, it is only 90% complete.[4] White matter fluctuates throughout life. Some areas of myelination require many years to complete with studies showing it can continue up until the sixth decade.[5] The myelination process proceeds from caudal to rostral structures or from phylogenetically older to newer areas of the brain; thus the frontal lobes are the last areas to myelinate. The postnatal driven myelination is what makes humans unique. The sequence of myelination in the human brain reflects the functional maturity not only in vision but also in other systems. With increased postnatal myelination, there is an increase in speed of neurotransmission or increase in bandwidth. It shows the vulnerability of the developing brain can be quite vulnerable to traumatic brain injury (TBI) because of incomplete myelination and myelin maturation variations with age. This may help explain why pediatric patients are described as "growing into their deficits" as they grow older.

Anatomic components

There are four anatomical components of the brain: the cerebral hemispheres, diencephalon, brain stem, and cerebellum. There are two cerebral hemispheres, the left and the right, each divided into four lobes, the frontal, temporal, parietal, and occipital lobes, each involved in different specific roles in vision. The left hemisphere predominately mediates language and verbal-associated function whereas the right hemisphere mediates visual spatial and nonverbal-related function. This is an oversimplistic division. An alternate view would be the left processing routine and the right novelty.[6] Figure 9.1 shows a lateral view of the cortex with named parts that can be used as a reference in the subsequent discussions of vision in this chapter.

The frontal lobe makes up one third of the cerebral hemisphere volume; it is complex, phylogenetically the most recent area to develop, and one of the last areas of the brain to myelinate. It is not a single functional unit. There are three major subdivisions, the precentral area, the premotor area, and the prefrontal area. The precentral and premotor areas work as a unit for planning and carrying out motor behaviors, including saccadic eye movements based on incoming sensory visual input. The prefrontal area is a more cognitive, sophisticated, integrated system involved in the highest level of visual and other sensory modality processing, resulting in action plans, incorporating meaning and intention.

There are three divisions of the prefrontal cortex based on their location: the dorsolateral, orbitofrontal, and medial frontal areas. The dorsolateral area is primarily involved in working memory and executive function, the orbitofrontal area in personality and self-control, and the medial frontal area in motivation for goal-oriented activities.

The temporal lobes are involved in visual pattern recognition and discrimination, memory acquisition, and emotional valence. The parietal lobes are involved in the processing of motion and location, multisensory integration, spatial perception, body representation, and preparation for visual motor integration. The entire occipital lobes are involved in reception and visual processing.

The diencephalon is the brain region above the brain stem, and it sits deep in the midline between the cerebral hemispheres. It has two major components: the thalamus and the hypothalamus. The thalamus gates sensory input to the cerebral hemispheres and is vital for processing of the attentional system. Pertinent visually related subcortical nuclei located in the thalamus are the pulvinar and the lateral geniculate body (LGN). The pulvinar occupies 40% of the thalamic volume, is located in the posterior portion, and is considered an association nucleus involved in complex visual function. The lateral pulvinar is linked with the posterior parietal, superior temporal, and medial and dorsolateral extrastriate cortices[8] as well as the superior colliculus.[9] It plays a role in orientation and processing visual information in the dorsal stream. The inferior pulvinar is linked with temporal lobe areas concerned with visual feature discrimination and extrastriate areas concerned with higher analysis of vision. It also receives visual input from the superior colliculus[9] in addition to direct input from the retinal ganglion cells.[8] The LGN is the other thalamic visually related nucleus that is part of the afferent system. The LGN also receives projections back from cortical-related visual areas, indicating that higher cortical processing can influence visual perception at an earlier level.

The hypothalamus is the other major part of the diencephalon. The hypothalamus has many distinct nuclei. It

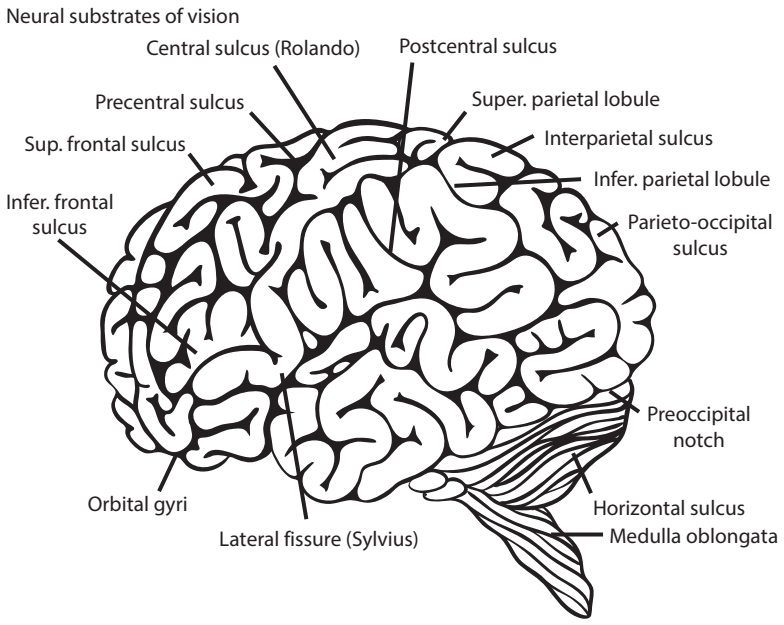


Figure 9.1 Lateral view of the cortex. (From Carpenter, M. B., and Sutin, J., *Human Neuroanatomy*, 8th ed., Williams & Wilkins, Baltimore, MD, 1983, p. 28. Reprinted with permission.)

maintains the body's internal state, serving as a thermostat to maintain body homeostasis. It houses brain centers for the autonomic nervous system and exerts higher level control of the neuroendocrine system, the latter of which has crosstalk with the neuroimmune system. It contains the suprachiasmatic nucleus, the pacemaker for the circadian cycle, which is entrained by light (nonimage) processed by the nonimaging retinal ganglion cells.

The brain stem has a diverse collection of nuclei related to the alerting arousal system that helps maintain attention as well as the awake state. These connect the brain stem with the thalamus, limbic system, and neocortex via the ascending reticular activating system. The reticular activating system is composed of three principal cell groups (nuclei): the cholinergic group with the pedunculopontine nucleus and laterodorsal tegmental nucleus, the noradrenergic group with the locus coeruleus, and the serotonergic group with the median raphe nucleus. Ascending projections from the reticular activating system to the intralaminar thalamus activate the cortex by nonspecific thalamocortical projections. In addition, a massive ventral projection from the brain stem bypasses the thalamus and terminates diffusely throughout the cortex to modulate cortical activity. These pathways also include dopaminergic neurons from the ventral tegmentum and periaqueductal gray matter and histaminergic neurons in the tuberomammillary nucleus. Other pertinent brain stem nuclei include the superior colliculus and the motor nuclei of the third, fourth, and sixth cranial nerves in addition to horizontal, vertical, and vergence gaze centers.

The cerebellum is involved with spatial organization and memory. It is also involved in refining motor control and probably motor learning. Although it only makes up about 10% of the total brain volume, it is densely packed with neurons (mostly tiny granule cells). The vestibulocerebellum participates in balance and spatial orientation. It mainly receives vestibular input along with visual and other sensory input. The spinocerebellum functions to fine-tune body and limb movements. It receives proprioceptive input as well as input from visual and auditory systems and the trigeminal nerve. It sends fibers to the deep cerebellar nuclei that project to the cerebral cortex and also to the brain stem to modulate descending motor systems. The cerebrocerebellum receives input exclusively from the cerebral cortex, especially the parietal lobe, via the pontine nuclei, and sends outputs to the ventrolateral thalamus. The cerebrocerebellum is involved in planning movement, evaluating sensory information for movement, and some cognitive functions, including emotional control. A defect in this system results in pseudobulbar affect.

Cortical organization

The cortex is at the top of the hierarchy for complex processing of visual information and integrating it with other sensory, motor, cognitive, and social/emotional domains. The cortex is needed for conscious awareness. The cortex covers all four lobes. The concept of the modular brain has changed over the past two decades to that of modular connectivity to explain behavior. The brain's organization of function is talked about in terms of modular units interconnected to form neural networks that serve different brain functions.[10]

NEOCORTICAL MODULES

The organizational blueprint of the brain begins in the neocortex, whose laminar structure consists of six layers, a ribbon over the cerebral hemispheres. Variations in the layers of cells are found in different parts of the cortex with those areas having similar columns of cells serving a specific function. These are called modules. As described later in this chapter, an example of a module would be the primary visual cortex (PVC) in the occipital lobe because of the specific organization of column cells serving specific functions, such as form, color stereopsis, and motion. There are other primary sensory areas, including the auditory, somatosensory, gustatory, olfactory, and vestibular cortices. These primary sensory areas project their specific modality to the surrounding association cortex for more complex processing. In vision, this would be the primary visual cortex or striate cortex to extrastriatal visual areas (see Figure 9.2). This results in different sensory-specific modality association cortices. These different sensory-specific association cortices then communicate with each other via bidirectional, divergent, and convergent fibers to form the posterior multimodal association area.

There are three multimodal association cortices: the posterior, anterior, and limbic association areas. These are shown in Figure 9.3. It should be noted that approximately 90% of the lateral surface of the cerebral hemisphere is covered with association areas. The posterior multimodal association area allows for spatial and temporal integration of all sensory modalities and is located in the posterior parietal lobe predominately in the angular gyrus. This is important for multisensory integration and spatial and language function. Figure 9.4 shows connections between the visual association areas with all three multimodal association areas. The anterior association area is located in the prefrontal area and allows for visual percepts to be incorporated into higher cortical function by determining which of the unimodal and multimodal inputs from other parts of the brain should be attended to at any specific time. The limbic association cortex, the allocortex, serves as a supervisor that processes feelings and emotion that interface between the external world and the internal self in addition to mediating memory. These supramodal areas, the anterior and limbic association areas, help bring our personal past and the present into the future. They bring explicit and implicit knowledge gained through past experience to bear on information processed in the here and now. The supramodal system can give rise to *de novo* creativity, ideas, thought, memory, motivation, and free will in the absence of sensory stimulation or action in the immediate present. The supramodal system is paramount to the genesis of our emotions. The higher

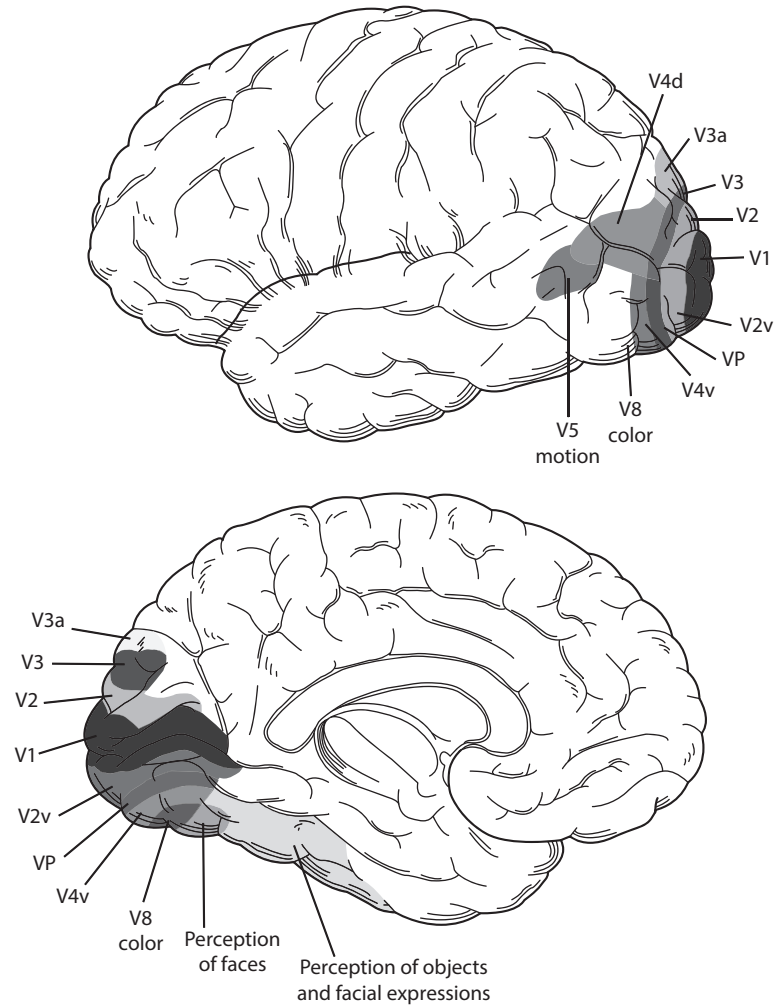


Figure 9.2 Principal visual areas in humans. (From Devinsky, O., and D'Esposito, M., *Neurology of Cognitive and Behavioral Disorders*, 2004, by permission of Oxford University Press.)

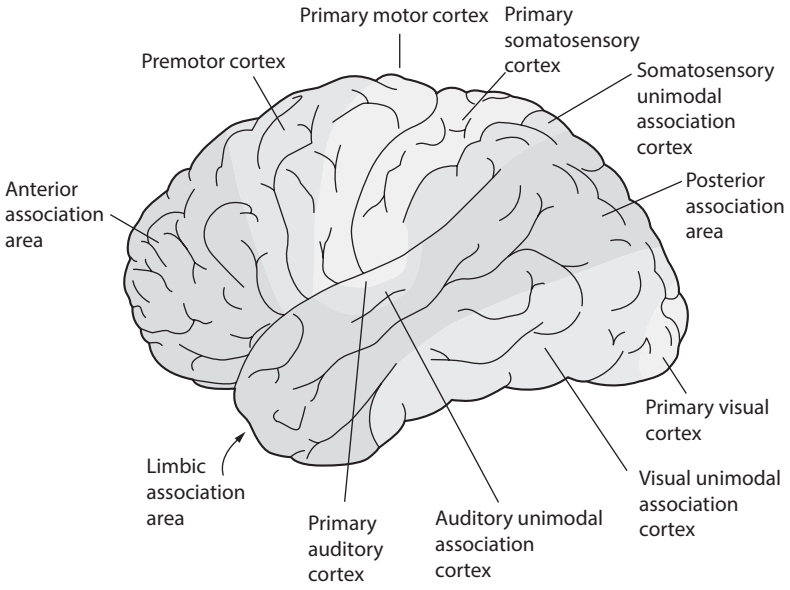


Figure 9.3 Different association cortices. (From Kandel, E. R., Schwartz, J. H., and Jessell, T. M., Eds., *Principles of Neural Science*, 4th ed., McGraw-Hill, p. 350, 2000. With permission.)

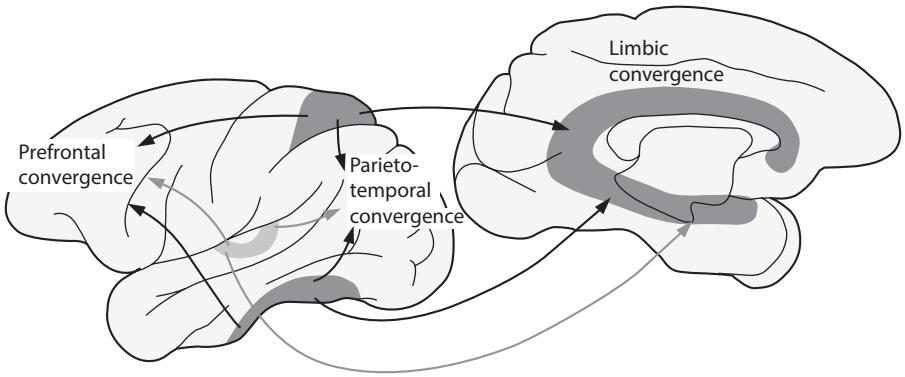


Figure 9.4 Visual association cortex connections to the anterior, posterior, and limbic multimodal association areas. (From Kandel, E. R., Schwartz, J. H., and Jessell, T. M., Eds., *Principles of Neural Science*, 4th ed., McGraw-Hill, p. 350, 2000. With permission.)

cortical functions are processes exclusively in the domain of the cerebral cortex.

NEURAL NETWORKS

Different cortical nodes include the primary unimodal association, multimodal association and supramodal cortices and are connected among themselves with the subcortical areas to form distributed neural networks to perform specific functions, including vision. In addition to the cortical areas, subcortical structures are involved in sensory, motor, and complex behaviors in a manner determined by both their intrinsic anatomical organization as well as their connectivity to the cerebral cortex.

These linkages are carried out by numerous axonal pathways located both in the cortex and subcortical white matter. These pathways consist of large groups of axons covered with a myelin coat and are identified as fasciculi, tracts, or bundles. Vision is created by the simultaneous integration of neural networks modulated by attention. These connections are bidirectional and multidirectional. They can converge or diverge from lower to higher centers, higher to lower centers, or can be collateral or spread out at the same level. This results in "top to bottom" or "bottom to top" processing. The organization of the white matter pathways begins in the cerebral cortex. Neurons within a specific cortical area give rise to three distinct categories of fiber systems that can be distinguished within the white matter beneath the gyrus. They are association fibers, striatal fibers, or subcortically directed fibers.[13] The association fiber tract can be divided into three categories: local, neighborhood, and long association fibers. The local association fiber system, or the U system, leaves a given area of the cortex and travels to an adjacent gyrus running in a thin identifiable band beneath the sixth layer of the neocortex. The neighborhood association fiber system arises from a given cortical area and is directed to nearby regions but is distinguished from the U fiber system that runs immediately beneath the cortex. The long association fiber system emanates from a given cortical point and travels in a distinct bundle leading to other cortical areas in the same hemisphere. The operation of long association bundles are mandatory for specific domains of vision. The locations of the more prominent fasciculi are shown in Figure 9.5. Their connectivity in the distributed neural networks is shown in Table 9.1. These are outlined in Filley's textbook, *The Behavioral Neurology of White Matter*.[14]

The superior longitudinal fasciculus links the superior parietal lobule and medial parietal cortex in a reciprocal fashion with the frontal lobe's supplementary and premotor areas. The superior parietal lobule codes movement and position-related activities of limbs in a body-centered

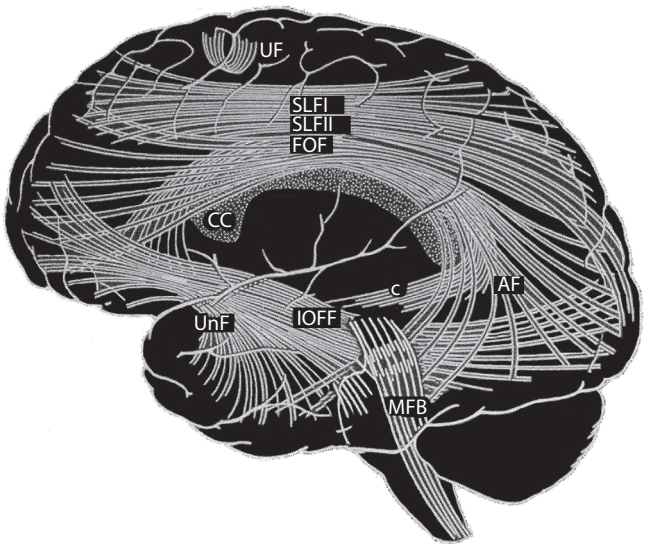


Figure 9.5 Major white matter tracts of the brain. CC = corpus callosum; UnF = uncinate fasciculi; IOFF = inferior fronto occipital fasciculus; UF = U fibers; SLFI = superior longitudinal fasciculus I; SLFII = superior longitudinal fasciculus II; FOF = fronto occipital fasciculus; AF = arcuate fasciculus; c = cingulate; MFB = medial forebrain bundles. (From Filley, C.M. *The Behavioral Neurology of White Matter*, 2001, by permission of Oxford University Press; *Neurobehavioral Anatomy*, Niwot, CO: University Press of Colorado, 1995. With permission.)

Table 9.1 Distributed neural networks

Domain	Gray matter structures	Connecting tracts
Arousal	Reticular activating system	Medial forebrain bundle
	Thalamus	Thalamocortical radiations
	Cerebral cortex	Fronto-occipital (right)
Visual orientation	Superior colliculus	Collicular–pulvinar
	Pulvinar	Pulvinar–cortical
	Post parietal lobe	
Spatial attention	Parietal lobe (right)	Superior longitudinal fasciculus II (right)
	Prefrontal lobe (right)	Cingulum (right)
	Cingulate gyrus (right)	
Visuospatial ability	Parietal lobe (right)	Fronto-occipital fasciculus (right)
	Frontal lobe (right)	
Higher order control of body centered action	Superior parietal lobe	Superior longitudinal fasciculus I
	Premotor areas	
Recognition	Temporal lobes	Inferior longitudinal fasciculus
	Occipital lobes	
Language	Broca's area	Arcuate fasciculus (left)
	Wernicke's area	Extreme capsule (left)
Memory	Medial temporal lobe	Fornices
	Diencephalon	Mamillothalamic tracts
	Basal forebrain	Septohippocampal tracts
Emotions and personality	Temporolimbic system	Medial forebrain bundles
	Orbitofrontal cortices	Uncinate fascicli

Source: Modified from Filley, C.M., *The Behavioral Neurology of White Matter*, 2001, by permission of Oxford University Press.

coordinated system, coordinating higher level visual, somatosensory and kinetic information regarding the trunk to the frontal lobe. Visual input is important to this fasciculus. The superior longitudinal fasciculus II links the angular gyrus and occipital–parietal area with the dorsolateral prefrontal cortex. It integrates polysensory information, is a component of the network of spatial awareness, and also plays a role in the visual and oculomotor aspects of spatial vision. The frontal occipital fasciculus originates in the occipital lobe, medial parietal lobe, and the angular gyrus, conveying information to the dorsal, premotor, and prefrontal areas. It is instrumental in processing visual information from the peripheral visual fields. The dorsal stream, which is discussed later in this chapter, is predominately composed of these three fasciculi. The inferior longitudinal fasciculus is a long association fiber system conveying visual information in a bidirectional manner between the occipital and temporal lobes, and its primary visual function is object, color, and face recognition in addition to object memory. This is the ventral stream of the visual system. The arcuate fasciculus links the caudal superior temporal lobe with the dorsal prefrontal area, mediating language function with input from the visual system. The cingulum bundle connects the caudate cingulate cortex with the parahippocampal and hippocampal areas that are involved in the motivational and emotional aspects of behavior as well as spatial working memory. The uncinate fasciculus connects the rostral temporal lobe with the prefrontal area and is involved in attaching emotional valence to visual information and recognition memory. An example of the striatal system would be the sagittal stratum, which contains the optic radiation. Besides these cortically derived white matter pathways linking the cortex with other areas of the hemisphere, other pathways exist connecting the hemispheres with each other, transferring the visual as well as other information from one hemisphere to another. They are called commissural fiber pathways with the main one being the corpus callosum. In summary, there are a multitude of neuronal assemblies that occur in the brain that are widely anatomically distributed yet functionally integrated to serve a specific domain.

ANATOMICAL DIVISIONS OF VISUAL SYSTEM

Image system

OPTICAL SYSTEM

The purpose of the optical system is to present a clear and undistorted image on the retina. Three major conditions must be in place for this to occur. The first is a refractory system provided by the cornea and the crystalline lens, which converge parallel rays from distant objects to a specific focus on the retina. The second involves accommodation that diverge light rays from near objects to a small point

focus on the retina. The third component is a transparent ocular media, the nonrefracting space occupied by the aqueous and vitreous, to project a clear focus on the retina. These supporting structures do not directly respond to light but rather facilitate the job of visual receptors that do respond to light. Problems with the eye refractory instrument, the lens and the cornea, typically result in blurred vision.

PRIMARY VISUAL SYSTEM

Retina

Vision begins in the retina, the retinogeniculocortical system. Unlike other sensory organs, the retina is part of the central nervous system, a myelinated tract extending from the diencephalon. See Figure 9.6 of retina. Light enters the eyes; passes through the optical system; and under perfect conditions with alignment, results in bilateral foveation. Light rays do not project to exact corresponding geographic regions on the retina because the two eyes are separated in space resulting in what is called "retinal disparity." If the difference is small enough, it can be resolved in the visual cortex, areas V1, V2, and V5 as noted later in the chapter, resulting in stereognosis. The brain is insensitive to light and can only respond to electrochemical events. The photoreceptors in the retinal pigment epithelium act as transducers between the physical world and the brain. The human retina is inverted, meaning light must pass through the ganglion and bipolar layers to reach the photoreceptors: the rods and cones. This design is efficient because these photoreceptors are metabolically active and receive their energy from the underlying blood supply in the choroid. The retinal surface is not flat but is 72° of a sphere. There are two types of photoreceptors on the neuroepithelial layer. The cones are a substrate for day vision, high visual acuity, and color. They contain three different photopigments with overlapping and spectral sensitivity ranges. Color vision is possible because the overlapping sensitivity ranges of these pigments permit color mixture to occur in the brain. Congenital color blindness occurs when one of these photopigments is absent. The rods contain a single photopigment, rhodopsin, which is maximally sensitive to dim light and not sensitive to color. The rods are a substrate for night vision, have low visual acuity, and are achromatic. There are estimated to be 126 million photoreceptors, 120 million rods, and 6 million cones that are stimulated by light passing its information to 50 million bipolar cells and, in turn, sending this message to 1 million ganglion cells. These photoreceptors are uniformly placed in all retinas. Cones are closely packed in the center area of vision, the fovea, reaching 200,000 cones per millimeter. This drops off exponentially from the center of the fovea. There are no rods in the fovea, and they are distributed in the peripheral retina. In the area of the fovea, the cell bodies of the more proximal layers are shifted to the sides enabling the visual image to receive its least distorted form. For the highest resolution of the visual image to occur, it is mandatory that the fovea be targeted upon by the visual stimuli. The majority of the ganglion and bipolar cells are located in the macular area of which part is the fovea. On

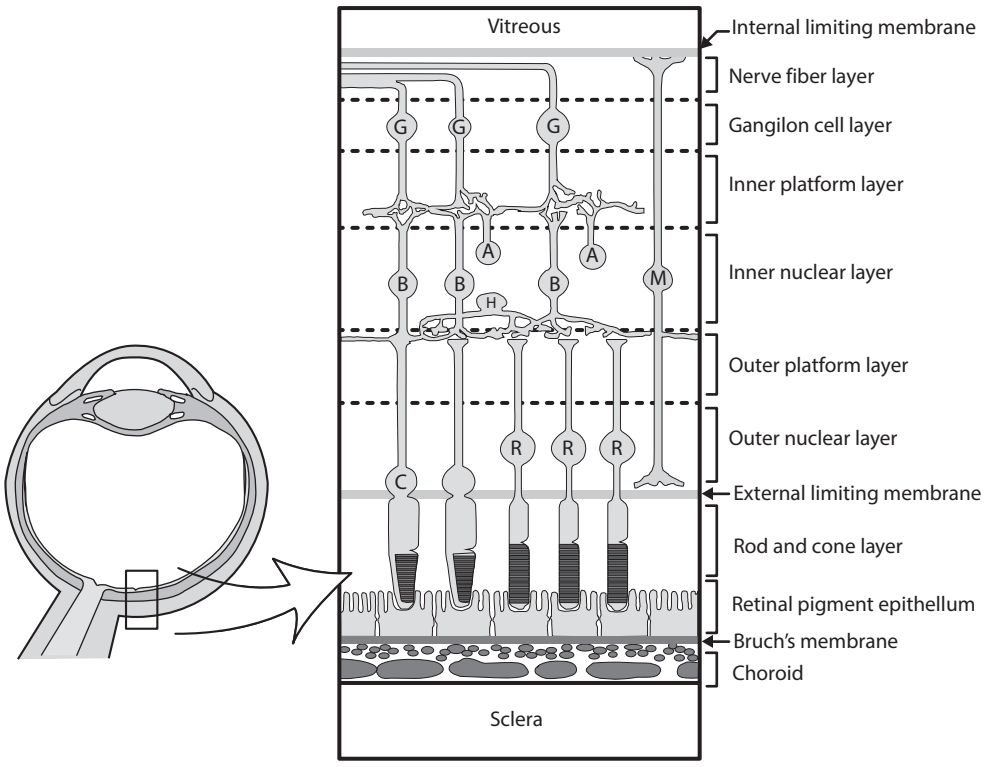


Figure 9.6 Layers of the retina. This cross-sectional view emphasizes synaptic connections. (From Trobe, J.D., *The Neurology of Vision*, 2001, by permission of Oxford University Press.)

the other hand, relatively few bipolar and ganglion cells are found in the periphery. Therefore, in the periphery, as many as 10,000 rods may feed information to a single ganglion cell. This organization of photoreceptor to ganglion cells provides for high temporal summation giving the rods high sensitivity to movement. These are the magnocellular ganglion cells. Because of the predominance of cones and their bipolar and ganglion cell connections in central vision, a one-to-one ratio occurs, allowing for high spatial summation. This results in a precise coherence between a point in a visual field and a point on the fovea, resulting in high visual resolution or high visual acuity at the expense of sensitivity. These are the parvocellular ganglion cells. In summary, the visual information is transmitted in the form of electrical signals from the photoreceptors to the retinal ganglion cells with modulation of signaling occurring as a result of the interneurons, altering the electrical signals by incorporating different spatial and temporal patterns of light stimulation. This relationship of connectivity allows visual space to be represented on the retina, resulting in the topography of vision, retinotopic mapping. Each point in visual space is topographically represented in a single region on the retina. The receptive field of retinal ganglion cells corresponds to patches of photoreceptors beneath them and connected to them; therefore, a lesion within the retina causes a visual field defect whose shape corresponds exactly to the shape of the lesion. This pattern of retinotopic mapping extends throughout the primary and secondary visual systems, allowing transmission of visual information to the brain that spatially corresponds to each point in space. A functional segregation occurs between the parvocellular ganglion cells (P) and the magnocellular ganglion cells (M) in the retinal ganglion layer. There is a difference in contrast sensitivity coded in the concentric off/on visual receptive fields. The P cells have smaller receptive fields, responding to patterns of high-spatial, low-temporal frequency with preprocessing for detail and color. The M cells have larger receptive fields responding to low-spatial, high-temporal pattern frequency involved in low contrast and large contour with early motion analysis. The axons of these retinal ganglion cells converge toward the optic disk where they emerge from the eye as the optic nerve. In the superficial retina between the ganglion cells and the optic nerve, the topography turns horizontal according to the geography of the axons of the retinal cells. Therefore, again, a lesion involving this area causes a visual field defect whose configuration is based on the configuration of the axonal bundles as they sweep across the retinal surface. Preprocessing has occurred as visual information from 126 million photoreceptors has been transmitted to over 1 million axons in the optic nerve.

Optic nerve/optic tract

The optic nerve passes through the sclera through a sieve-like structure called the lamina cribrosa. Because there are no photoreceptor cells at the optic disk, a blind spot is produced in the field of vision. Each optic nerve contains retinotopic maps, representing both heminasal and hemitemporal visual space of its companion nerve. The optic nerve passes posteriorly through the orbit and enters the cranial cavity through the optic foramen and joins its fellow of the opposite side to form the optic chiasm. At the optic chiasm, a partial decussation of fibers from the two sides takes place. Fibers from each eye destined for either side of the brain are sorted out and rebundled, forming the optic tracts, which carry information from the contralateral visual fields of each eye.

Information from the right hemifield is routed to the left side of the brain, and information from the left hemifield is routed to the right side of the brain. Each optic tract, in turn, partially encircles the cerebral peduncle and passes to three subcortical structures: the pretectum, the superior colliculus, and the LGN. The majority of the axons of each optic tract proceed to the LGN located in the thalamus. An abbreviated tract, however, extends more rostral, bifurcating to form two retinomesencephalic tracts, one to the pretectum and the other to the superior colliculus (see Figure 9.7).

Ninety percent of the retinal axons terminate in the LGN. Conversely, only 10% that synapse in this nucleus are received from the retina whereas 90% are received from other areas, predominately the cerebral cortex. This suggests that although the retinogeniculate connection is the driver, the corticogeniculate link does a great deal of modulation at this very early stage of visual processing. As the optic tract enters the LGN, there is a continuation of the retinotopic representation of the contralateral visual field. In humans, the LGN contains six layers of cell bodies separated by interlamellar layers of white matter or axons. The layers are numbered from one to six, ventral to dorsal. The two most ventral layers of the nucleus are known as the magnocellular layers with the main input coming from the M-ganglion cells. The four dorsal layers are known as the parvocellular layers and receive input from the P-ganglion cells. Both the magno- and parvocellular layers include the same concentric fields with off/on center cells that were present in the retinal ganglion cells. Further, axonal fibers in the ipsilateral and contralateral eyes area segregated in the layers of the LGN. Layers one, four, and six include the termination of axons from the contralateral eye whereas layers two, three, and five contain axons from the ipsilateral eye. Although each layer does contain retinotopic maps, the retinal space is not represented isometrically as the foveal region. The foveal region occupies less than 10% of the retinal surface and projects to 50% of the surface area of the LGN.[15]

Mesencephalic tract

After sending most of its axons to the LGN, the optic tract proceeds rostrally to the mesencephalon. The first tract goes to the pretectal nucleus, whose cells project to the ipsilateral Edinger–Westphal nucleus and then to the contralateral Edinger–Westphal nucleus via the posterior commissure. Preganglionic neurons in both Edinger–Westphal nuclei send axons out of the brain stem in the oculomotor nerve to innervate the ciliary ganglion. This ganglion contains

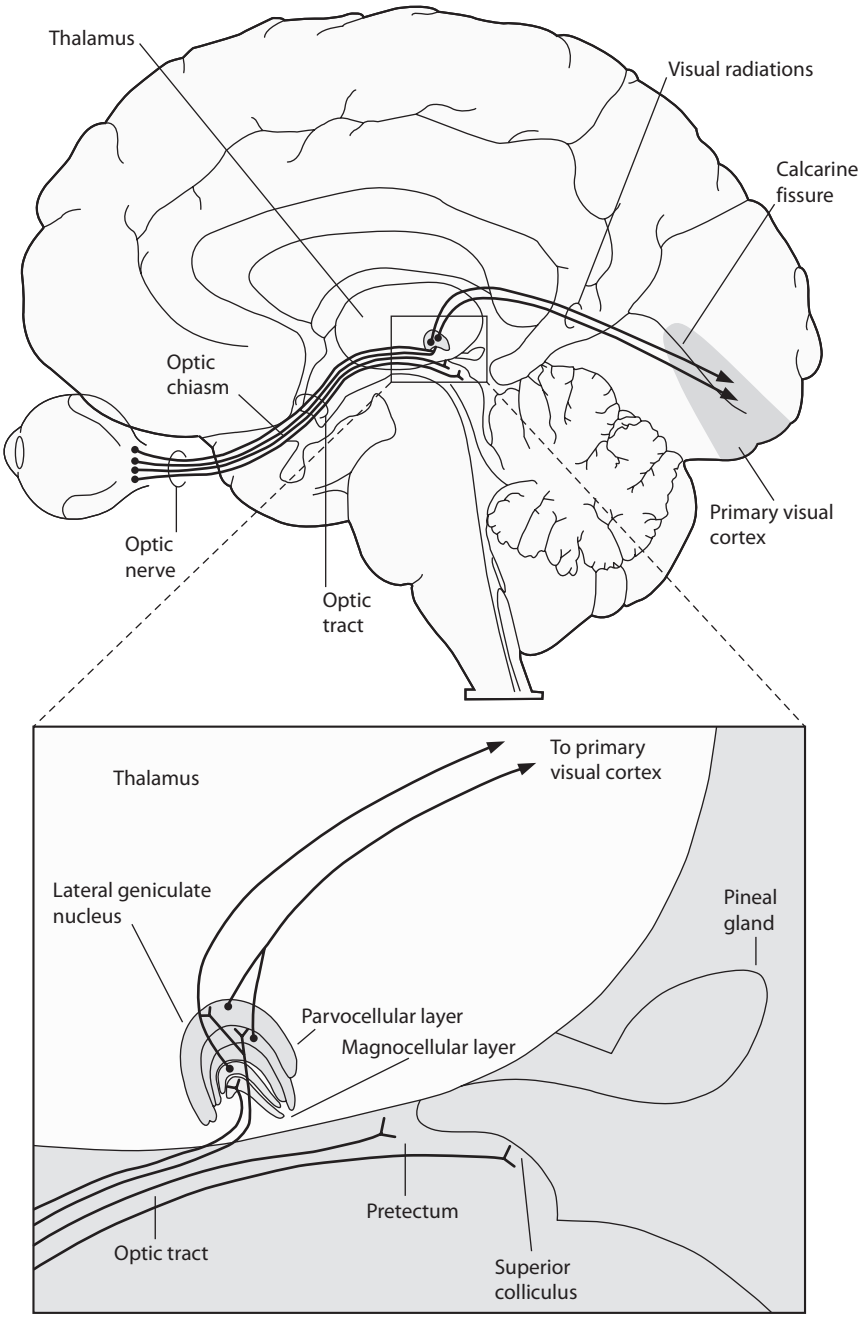


Figure 9.7 Route of the optic tract to the LGN, pretectum, and superior colliculus. (From Kandel, E. R., Schwartz, J. H., and Jessell, T. M., Eds., *Principles of Neural Science*, 4th ed., McGraw-Hill, p. 527, 2000. With permission.)

the postganglionic neurons and innervates the smooth muscles of the pupillary sphincter that constricts the pupil. Pupillary reflexes are clinically important because they indicate the functional state of both the afferent and efferent pathways. This connection is important for the accommodation reflex—that is accommodation, convergence, and miosis. The remainder of the optic tract also goes to the mesencephalon to the superior colliculus. It is a nuclear structure of alternating gray and white matter. These retinotectal fibers project into its superficial layers and convey a map of the contralateral space. The superficial layers also receive visual input from the visual cortex whereas cortical input from other sensory modalities project to deeper layers. Under the control of these cortical connections, multisensory and spatial integration occurs.[16] Thus, cortical control is necessary to process more than one modality in one specific time. However, the superior colliculus also operates as a unimodal system for reflexive orienting of the eyes and head using direct retinotectal information. This allows for quicker response times in survival situations. In everyday situations, the superior colliculus is influenced by control of the frontal eye field in generating and controlling eye and head movements. The superficial layers of the superior colliculus are the origin of the connection linking

the pulvinar, which, in turn, projects to the cerebral parietal area, which is the neural network responsible for the orientation of visual attention.

OPTIC RADIATION

The optic radiations connect the LGN with the primary visual cortex. This is a large fiber tract and, surprisingly, the majority of its fibers are not part of the geniculocortical tract but come from thalamic nuclei and visual cortex. As they leave the LGN, they occupy the posterior limb of the internal capsule. The fibers then sweep around the lateral ventricle to terminate in the PVC, continuing to transmit visual information from the contralateral visual field. The fibers representing the inferior half of the retina are located more ventrally than those representing the superior portion of the retina. Those axons representing the inferior retinal input end beneath the calcarine fissure whereas those representing the superior retinal input terminate above the calcarine fissure.

Primary visual cortex

The primary visual cortex (V1) is known as the striate cortex and serves as the last formal station for the primary afferent visual system. V2 and V3 are adjacent and are discussed with V1 because they form an advanced unit carrying out higher visual processing. Each hemisphere's V1 receives information directly from the ipsilateral LGN, conveying representations of the contralateral visual field and representing each eye separately. Eighty percent of the PVC is buried in the calcarine fissure, anteriorly extending to the parieto-occipital fissure and posterior to the occipital convexity. Retinal space continues to be unrepresented isometrically. The foveal area, which occupies less than 10% of the retinal surface, continues to be over-represented in the PVC as it is in the LGN because of the ratio of cones to retinal ganglion cell connections. The caudal 50% of PVC volume encodes representation from the foveal area, the central 10° of the visual field. The middle 40% of the PVC contains information from 10° to 60°, eccentric to fixation with the rostral 10% of the PVC encoding the peripheral 60° to 90°.[15] Input from the LGN enters layer four of the PVC. Segregation of the P and M cells continues as they terminate in different sublayers of the primary visual cortex 4Cb and 4Ca, respectively. V1 is organized into vertical columns, meaning they form perpendicularly to the cortical layers. Single and complex neurons fill these columns. The simple cell's receptive field changes from concentric to rectangular in shape with contrast edge sensitivity response, changing from a spot to a bar. These orientation columns are the hallmark organization of the PVC. They are thus tuned to a response to a specific orientation. These are specific columns for each 10% degree in orientation.

Numerous single cells project to a complex cell. Their receptive fields are larger and do not have the off/on regions. Although these fields have a critical axis of orientation, the precise position of the stimulus within the receptive field is less crucial because there are no clearly defined off/on regions. When movement occurs, receptive fields will be encoded. Blobs that process early analysis of color occasionally interrupt the systematic shifts and axis orientation from one column to another. Hypercolumns are formed that are aggregates of columns of cells sensitive to all possible orientation of a particular stimulus located in a particular region of the visual space. Inputs from the right and left eye from alternating hypercolumns converge to form ocular dominance columns. This is the first time the input from both eyes come together and are involved in the initial resolution of retinal disparity. Horizontal layers interconnect all hypercolumns and bring together all the visual representations of the visual field. This allows for the pieces of a puzzle to be put together to create an internal representation of the whole contralateral visual field. The orientation column input for form analysis is forwarded to the pale stripes in V2, the ocular dominance columns for motion and stereopsis to the thick dark stripes in V2, and the blob system to the dark thin stripes in V2 for color analysis (see Figure 9.8). Amazingly, poorly organized visual representations based on changes of response to edge contrast sensitivity are projected from the retina to V1 where they are deconstructed into various line orientations by single and complex cells and then reconstructed by hypercolumns of cells, thereby becoming the three-dimensional world that we call vision. V1 has numerous connections not only with the extrastriate areas, but also with numerous other higher cortical and subcortical units, the latter including the superior colliculus, pons, pulvinar, and LGN.

SECONDARY VISUAL SYSTEM

Ventral stream

The secondary visual system begins after exiting the PVC. Two major pathways are formed. Those are the P cells, i.e., the ventral pathway, and those of the M cells, i.e., the dorsal pathway. The ventral pathway passes through V2 and V3 and on to other extrastriate visual processing areas. The ventral pathway is predominately the inferior longitudinal fasciculus (ILF). It is known as the "what" pathway because its main function is object recognition and discrimination. After exiting V3, the ILF extends into the ventral part of the temporal lobe where it is composed of two limbs: a vertical limb and a horizontal limb.[13] In general, however, in talking about the ILF, the horizontal limb is the main functional component. The horizontal limb extends rostrally into the temporal lobe up to the area of the uncinate fasciculus, passing through the fusiform gyrus, inferior temporal lobe, and parahippocampal gyrus. Extrastriate visual processing areas include V4 for object discrimination and partial form recognition, and V8 and V4 for color perception, the fusiform gyrus for facial recognition, and the inferior temporal area for more complex pattern recognition, including object recognition as well as scene and place recognition. As the ventral stream extends further into the anterior temporal lobe and the parahippocampal areas, it connects with the hippocampus and amygdala in the limbic system to attach

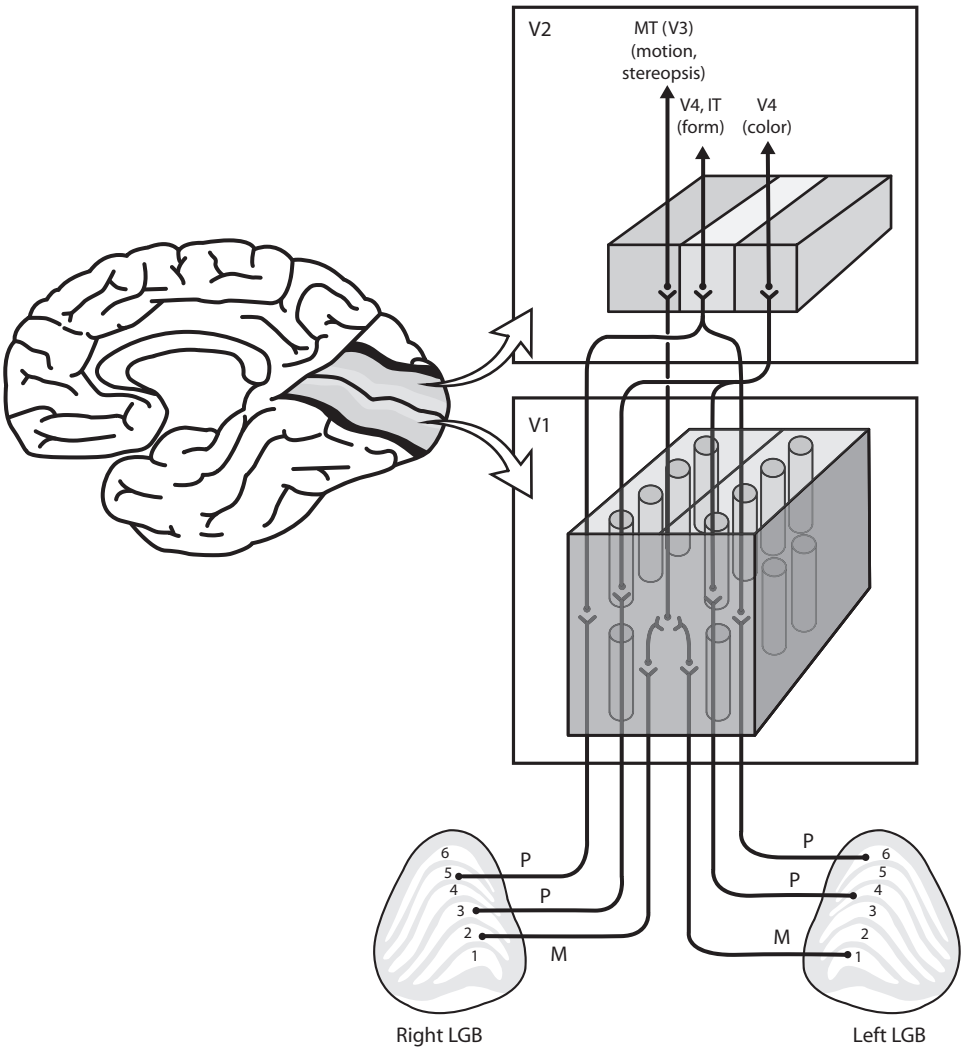


Figure 9.8 Feature processing in the visual cortex. Form, color, motion detection, and depth perception (stereopsis) are encoded in separate channels. (From Trobe, J. D., *The Neurology of Vision*, 2001, by permission of Oxford University Press.)

memory and emotional salience. This allows for recognition of facial expressions. Fibers traveling in the vertical limb of the ILF terminate in the lower bank of the superior temporal sulcus, or V5,[13] illustrating one of the various connections between the ventral and dorsal streams.

Dorsal stream

The dorsal stream extends V1 and passes through V2 and V3 and then projects through the posterior, middle, and superior temporal lobe (MT/MST complex), moves up to the angular gyrus, and then more dorsal to the intraparietal sulcus just beneath the superior parietal lobule. The dorsal stream is basically composed of three long association tracts: the FOF, SLFI, and SLFII. All these fasciculi connect the posterior parietal lobe with areas of the frontal lobe, including the anterior association area and the motor association areas, including the frontal eye fields. The dorsal stream predominately encodes visual representation in the contralateral peripheral visual field involved in the perception of motion and location, is instrumental in spatial cognition and multisensory integration, and codes for preparation of visuomotor integration, including saccadic eye movements. This is discussed later in this chapter in the section under Higher Visual Processing (see Figure 9.9).

Nonimage system

RETINOHYPOTHALAMIC TRACT

The nonimage visual system has one major pathway, the retinohypothalamic tract (RHT).[17] A light source emanates light waves. The majority are processed by the rods and cones with visual information sent to the retinal ganglion cells for processing and segregation; however, a small component of the retinal ganglion cells, estimated to be 2%, receive and process photic vision signals directly via an opsin-contained molecule unique to their cell type, melanopsin.[18] It is fundamentally a sensory photosensitive

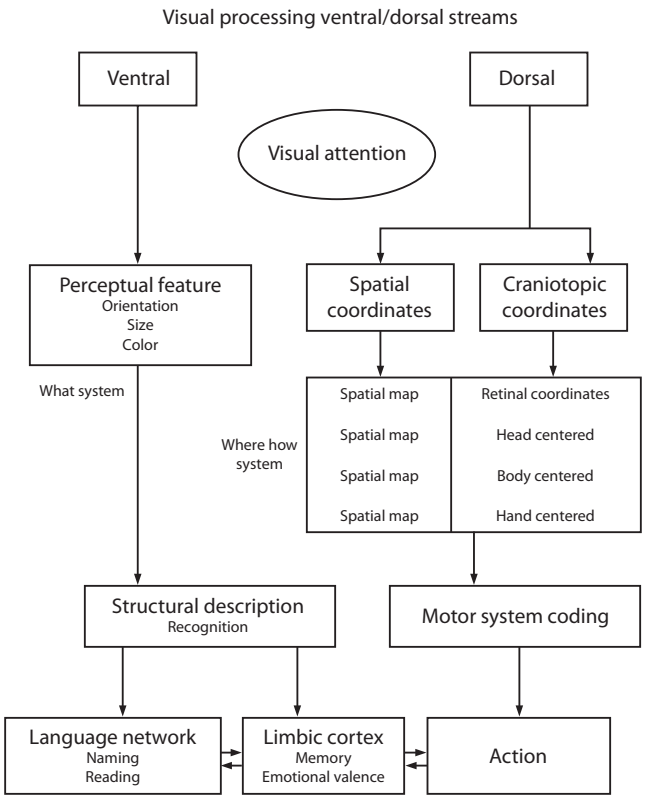


Figure 9.9 Visual processing in ventral and dorsal streams.

pigment that causes initial phototransduction to light. These specific retinal ganglion cells are represented over the entire retinal surface. Their axons are bundled together to form the RHT, which monosynaptically connects with the suprachiasmatic nucleus in the hypothalamus. The RHT travels in the optic nerve to the optic chiasm and then extends up to the hypothalamus to terminate in the suprachiasmatic nucleus although it has other connections, including to the paraventricular nucleus.[19] The suprachiasmatic nucleus is a pacemaker for the circadian rhythm, the innate daily rhythm of the awake/sleep cycle. The period of the natural light/dark cycle is close to 24 hours. The light information processed in the RHT entrains the circadian cycle via its input to the suprachiasmatic nucleus. Blind individuals still preserve the circadian rhythm because these type of retinal ganglion cells are preserved whereas the blindness results because of impairment of the rods and cones.

PRINCIPLES OF VISUAL SYSTEM ORGANIZATION

Vision is a major functional system in the brain. Kandel's book *Principles of Neural Science* describes the five principles governing the organization of the brain's functional systems.[12] The first is that each functional system involves several brain regions that carry out different types of information processing. An example in the visual system would be the retina, superior colliculus, LGN, pulvinar, and PVC. These are not merely relay stations in that modification of visual information occurs at each step. The second principle is that identifiable pathways link the components of the functional system. In the case of vision, the major pathways include the retinogeniculocortical pathway and the dorsal and ventral streams. The third principle is that each point of the brain projects in an early fashion onto the next via topographic maps. Retinotopic maps are the visual maps that fulfill this criteria. The fourth principle is that functional systems are hierarchically organized. In vision, the hierarchical arrangement for more selective and advanced processing begins in the retina and passes via the retinocortical tract to the dorsal and ventral streams. In addition, there is also parallel processing with the magnocellular and parvocellular systems processing for motion, color, and form, respectively. The last principle states that one side of the brain controls the opposite side of the body, which is important in visual brain representations in that one side of the brain represents the contralateral visual field.

FUNCTIONAL COMPONENT OF THE VISUAL SYSTEM

Reception

PRIMARY VISUAL SYSTEM

The optic system, the oculomotor system, and the primary afferent visual system provide for the function of visual reception. Visual reception is the ability to see, fixate, fuse, focus, and move the eyes to the object of regard and send the signal in its purest form from the retina to the PVC. The optic and primary afferent visual systems have already been discussed.

OCULOMOTOR SYSTEM

Visual reception is often thought of as a solely sensory function but has a significant motoric component, the oculomotor system. This is the gaze system, the visual fixation system that allows for bilateral foveation of the desired target. It is dependent upon full fields of vision that are selected from the attention system of the brain. Eye movements play an important role in how we perceive and interact with the environment. More is known about the cortical control of the oculomotor system than any other motor response. The limited degrees of freedom in the natural range of eye movements simplifies this study when compared to other movements of limbs containing multiple joints. Furthermore, the existence of parallel subsystems of ocular motor response reveals a sophisticated repertoire of responses dependent upon the type of sensory input and volitional state of the individual. The gaze system has two synchronized components: the supranuclear and infranuclear divisions.

Supranuclear system

The cortical or supranuclear influence on gaze is carried out by six distinct neural networks: 1) the saccadic eye system directs the fovea from one object to another object of

interest; 2) smooth pursuits hold the image of a moving target on the fovea; 3) the vergence system acts to move the eyes in opposite directions (i.e., convergent and divergent) so that the image of a single object in space can be placed simultaneously on the fovea; 4) the vestibulo-ocular system holds images still on the retina during brief head movements driven by signals of the vestibular system; 5) The optokinetic system holds the image still insofar as possible during sustained head rotation or watching a sustained stimulus going by, such as a train; and finally, 6) the fixation system holds the fovea in place on a stationary target. These complex supranuclear networks result in eye movements coordinating whole muscle groups. They determine the direction of movement but not the amplitude. With the exception of the vergence system, supranuclear eye networks mediate conjugate eye movements. Supranuclear damage does not lead to diplopia but to restrictions of conjugate gaze, such as horizontal or vertical gaze palsy. The higher cortical centers that influence gaze specify only a desired change in eye position as determined by visual information of the desired environmental stimulus. The six distinct supranuclear gaze systems have different functions; therefore, they have different complex neural networks whose description is beyond the scope of this chapter.

The saccadic system is the most important and well studied in TBI. The cortical control is exerted by the posterior parietal cortex and its connection to the frontal eye fields, allowing feedback to the superior colliculus in the brain stem. The superior colliculus is the motor commander of the horizontal gaze center located in the pontine reticular formation and the vertical gaze center in the mesencephalic reticular activating system. These gaze centers, again, control the direction but not the amplitude of eye movements. In addition, the superior colliculus, through multisensory integration (vestibular and proprioceptive), coordinates movements of head position and eyes to keep the stimulus on the fovea in the visual field.

Infranuclear system

The supranuclear gaze system controls the infranuclear gaze system. The infranuclear oculomotor system is a complex motor system requiring the coordination of 12 muscles to move the eyes. These muscles are well known and rotate the eye in the orbit by abduction, adduction, elevation, depression, intorsion, and extorsion. This system, again, controls amplitude of movement, but the gaze center predominately controls direction. This system consists of the motor nuclei and cell extensions or cranial nerves III, IV, and VI. Innervation of extraocular muscles is ipsilateral to cranial nerve nucleus III and VI and contralateral to cranial nerve IV. Weakness of one of the muscles innervated by these cranial nerves will result in a misalignment of the eyes and create diplopia. In addition, cranial nerve III carries parasympathetic fibers that supply the smooth muscle of the ciliary body for accommodation and the iris sphincter for pupillary constriction. Abnormalities of this system result in problems with accommodation, miosis, and convergence insufficiency.

Attention

Attention is the foundation for cognition. Attention is a modular process allowing us to process all information available for review in the environment. Attention is a matter of organizing multiple brain centers in concert with the task at hand. The brain's capacity for processing not only visual but other sensory input is limited due to the lack of receptive capacity for evaluation of the environment. Thus, attention serves as a filter, selecting salient signals for further processing. Humans have the ability to temporarily hold more than one stimulus at a time. Thus, attention can be divided into a variety of phenomena, such as single, sustained, or divided attention. The textbook *Neurology of Cognitive and Behavioral Disorders* by Devinsky and D'Esposito[20] provides a schematic approach to the neural circuitry of attention (see Figure 9.10). Attention is divided into three hierarchically organized neural networks, the arousing alerting network, the orienting network, and the selective attentional network. These are composed of multiple ascending and descending connections processing for the seamless modification of visual information providing for both bottom-up and top-down processing.

AROUSAL/ALERTING

The arousal alerting network is a diffusely distributed attentional system located in and extending from the brain stem to the intralaminar thalamus, neocortex, and limbic system. It is a total subcortical network. It mediates the awake state and is involved in the modulation of conscious awareness. Its major component is the reticular activating system, a mixture of various nuclei associated with specific transmitters with both ascending and descending tracts. Important nuclei in this system include the locus coeruleus (noradrenergic), the pedunculopontine and lateral dorsal tegmental nuclei (cholinergic), the median raphe (serotonergic), the substantia nigra and ventral tegmental area (dopaminergic), tuberal mammillary body neurons (histaminergic), and hypothalamic neurons (orexinergic). These directly modulate both the thalamic and extrathalamic systems.

ORIENTING NETWORK

The anatomical network for visual orientation involves the superior colliculus, pulvinar, and the posterior parietal cortices, a subcortico-cortical unit. Visual orientation refers to attending to contralateral space or markers in it. This is a preattentive process, the unconscious evaluation of the environment. All available visual information is preattentively screened. The superior colliculus attends and records information from the ipsilateral space via modulating reflexive eye movements toward the stimulus (overt) or without eye movement (covert). The information is then bundled and projected to the pulvinar of the thalamus. The pulvinar again filters out irrelevant stimuli. This elevates response to include the target and assists in covert orienting to retain those stimuli with high salience in relevance to the anticipated task at hand.

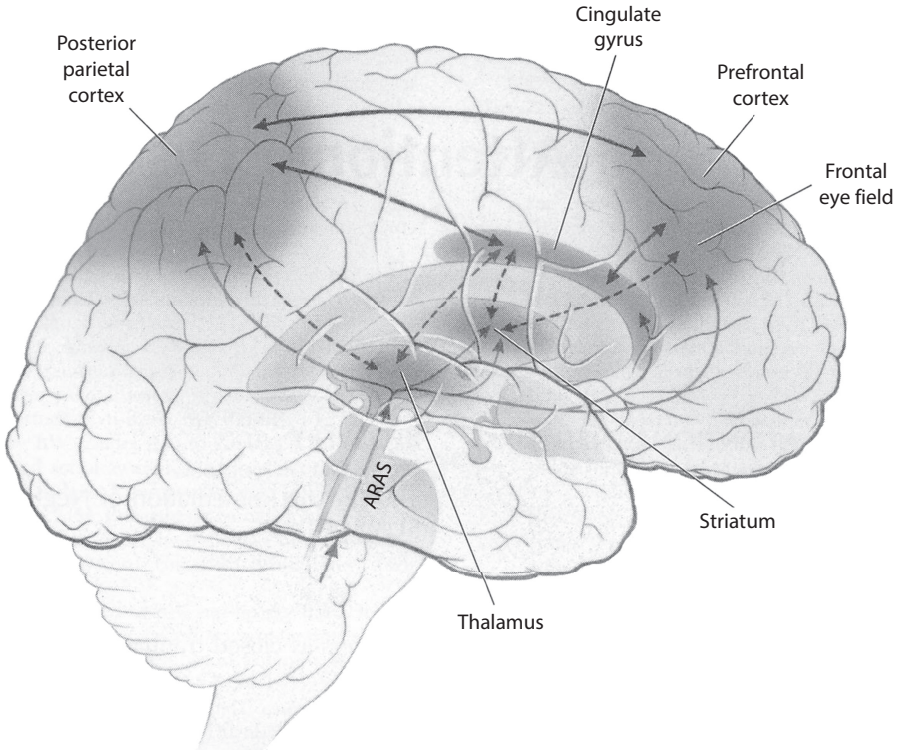


Figure 9.10 Functional anatomic networks of attention. ARAS = ascending reticular activating system. (From Devinsky, O., and D'Esposito, M., *Neurology of Cognitive and Behavioral Disorders*, 2004, by permission of Oxford University Press.)

SELECTIVE ATTENTION NETWORK

The selective attention network is a total cortical network involved in voluntary top-down processing. This network includes the association cortices and the posterior parietal lobes, dorsolateral frontal lobe, and the anterior cingulate cortex of the limbic system. The posterior parietal cortex mediates visual attentional function, the dorsolateral frontal lobe mediates motor and executive attentional function, and the anterior cingulate mediates motivational aspects of selective attention or salience. The major long association tract connecting the anterior and posterior association areas in selective attention is the superior longitudinal fasciculus. Each hemisphere directs the attentional focus to the contralateral hemispace, both personal and extrapersonal. The left posterior parietal lobe disengages from objects whereas the right posterior parietal lobe predominately disengages from location. Sustained attention is more under the control of the frontal areas, predominately the right hemisphere as well as the anterior corpus callosum.

The complete functional organization of the visual attentional system is complex, and its exact mechanisms remain elusive. It is the binding or ability to simultaneously bring online neural circuits that mediate form, color, and spatial representation. The selective and sustained attentional systems allow this internal representation to enter the realm of consciousness and to proceed as a unified whole. Cognitive control of the anatomical functional unit of attention is carried out via both endogenous, voluntary, top-down cortically controlled processing and endogenous, automatic, reflex, bottom-up control, which is stimulus driven. The master switch that controls attention is unknown, but it has been suggested, as noted earlier, that the prefrontal cortex is an important area. There is, however, controversy as to whether there is a diffusely distributed system of master control throughout the cortex and thalamus or a smaller set of neurons acting as a spotlight of attention. Crick suggested that the claustrum is a likely candidate for the master switch.[21] To further complicate the issue, attention can not only be focused, but also diffuse with flexibility existing in regards to the attentional focus. If the master switch does exist, where does it report? What turns the master switch off and on, creating a subconscious to a conscious experience? Switching definitely occurs as demonstrated by a simple exercise in studying binocular rivalry. Two different images, one vertical stripes and the other horizontal stripes, can be presented to an individual simultaneously in such a manner that each eye can only see one set of stripes. The person may see the plaid design or alternate back and forth, seeing the vertical or horizontal stripes. This is an example of both binocular competition and the switch of attention.[22]

Higher visual processing

Higher visual processing is the last but most complicated component of the functional visual system. Elementary visual representation based on contrast luminance and sensitivity response with different temporal and spatial

patterns begins in the retina. The M and P cellular systems provide channels for carrying visual information for form, color, and motion. Visual representations are reconstructed in the PVC, and more refined analysis occurs in the orientation columns, ocular dominance columns, and blobs for form, stereopsis, and color, respectively. The retinal disparity factor is resolved.

From the PVC, the P cellular system emerges as the ventral stream and the M system as the dorsal stream. Hierarchal processing continues with the extraction of progressive, more complex and global features. Retinotopic mapping is less specific, allowing for more global feature processing. An example would be that the orientation of an object in space becomes secondary to its shape. Ungerleider and Mishkin proposed two parallel visual streams in 1982.[23] Neurons included information in the ventral stream for orientation, size, shape, and color, referred to as the "what" stream. Neurons in the dorsal stream code for motion, movement, and location, referred to as the "where" system. In 1992, Goodale and Milner modified this model contrasting perception versus action for the ventral and dorsal streams, respectively.[24] Rizzolatti and Matelli, in 2003, further modified the dorsal stream so that two of its own components included the dorsal and ventral streams.[25] The ventral/dorsal stream was to code for spatial perception and action understanding whereas the dorsal/dorsal stream coded for action online.

VENTRAL STREAM

The ventral stream, the occipital temporal pathway, extends V1 to V2 to V3 for higher visual analysis, as described earlier, and onto V4. Neurons in this region are sensitive for allowing to differentiate figure from ground and formulate initial form by evaluating length, width, and orientation for pattern formation. A breakdown in this system results in apperceptive visual agnosia, an incomplete perception of form or object. In the posterior fusiform gyrus area is V8, the color area.[26] This processes visual constancy for perception of color. The color area is close to an area that processes face recognition. A lesion in the latter area results in prosopagnosia. More forward in the temporal area, higher level analysis of more complex patterns occurs, allowing for object, place, or scene recognition. The anterior ILF ends near the hippocampal and amygdala area, which is the limbic association area, which gives memory and emotional salience to the visual representation. This allows one to recognize facial expression.

DORSAL STREAM

Whereas visual perception is more concrete in the ventral stream, it is more abstract in the dorsal stream. This is secondary to the different sensitivity of neurons in the dorsal stream. Neurons in the dorsal stream are more sensitive to high temporal frequencies and are specialized for spatial perceptions in different ways. The visual field representations are broader, extending outwards up to 90° whereas the ventral stream responds only up to 35° to 40° of the visual angle. They are also specialized for detection and analysis of moving stimuli, including speed and direction. Other specific properties are that for not only motion, but rotation and depth.[27] The dorsal stream is composed primarily of three long association tracts, fronto-occipital fasciculus (FOF), superior longitudinal fasciculus 1 (SLFI), and the superior longitudinal fasciculus 2 (SFLII). The dorsal stream extends from V1 to V2 to V3 and on to V5 (MT/MST complex). The MT–MST complex of the cortex specializes in the perception of motion and is crucial for the control of optic flow.[28] The FOF extends forward from MT/MST to the prefrontal cortex in the anterior association area and to the motor association areas processing visual spatial ability, providing input from the peripheral visual fields in preparing for action.

BEYOND THE VENTRAL/DORSAL STREAM

Beyond V5, the next major area is that of the angular gyrus. The angular gyrus is in the heart of the posterior association area where multisensory integration occurs and also is important for spatial perception. In this area, SFLII projects forward, connecting the posterior association areas with the anterior association areas and the limbic association areas. This is a main component of visual spatial attention and plays a role in visual and ocular aspects of spatial awareness. Space is defined as boundless 3-D space in which objects and events have related position and direction. It serves as a background to place and locate visual representations. It has vertical, horizontal, and radial axes. Tasks have been developed that are available to assist at the bedside to differentiate disorders of these spatial axes.[29] Our subjective experience strongly suggests that we have direct access to a single, coherent, and overlapping representation of space as it is perceived as an instant, seamless entity. There is, however, no evidence for the existence of a single topographic representation of space available for incorporating each type of sensory input and generating every type of motor output. Space is constituted by a multiple representation of space in a variety of coordinate frames and linked to separate output systems to guide specific motor effectors. Hemispheric control of attention is governed by hemispace.[15] Visual hemispace is based on the orientation of head and body coordinates (craniotopic) with visual contributions to the retinotopic coordinates. Space has two components, the contralateral half of the body (personal) and extrapersonal space. Parietal and frontal cortices construct multiple spatial representations in order to carry out attentional and sensory motor goals. Spatial cognition has three progressive stages: a dedicated perceptual attentional stage, a representative stage, and a motor-attention component.[30] Visual cognition is involved in the visual perceptual aspects, i.e., the visual representative component, but only contributes to the multisensory nature of the input and output systems. The SFLII provides the visual component for spatial cognition specifically in this area by converting retinotopic to craniotopic coordinates. The right hemisphere extends control predominately

over the left hemispace but also partially over the right hemispace whereas the left hemisphere governs only its contralateral hemispace. Thus, the right posterior parietal area is dominant for spatial attention.

The remainder of the dorsal stream extends upward as SLFI, passing through to the area of the intraparietal sulcus, the bottom border of the superior parietal lobule, and then passes forward to the frontal portion of the brain to the supplementary eye and premotor areas. Housed in the superior parietal lobule is a body representational map. It is composed of craniotopic coordinates based on the orientation of the head and body. Three major inputs control body posture representation, those being visual, proprioceptive, and vestibular. Body schema provides an online representation of sensory input that articulates the spatial system and permits one to localize stimuli both in respect to the body surface and body position in space. This online representation of the body is real time and is coded to perform tasks and accomplish goals. This gives us knowledge of where our body is in space and what is in space by conveying high-order polysensory information regarding head, trunk, and limbs to the frontal lobe for action. There are two basic spatial reference frames. The first frame, centered on one's current location, is an example of egocentric or viewer-based frame, in which locations are represented relative to the observer. The second reference frame, the allocentric frame, is in use when locations are presented in reference frames independent of the observer. This is mediated in the frontal lobe whereas the egocentric reference frame is mediated in the parietal lobe.[27] Thus, there is a diversity of spatial representations in both the parietal and frontal lobes, constructing multiple spatial representations in order to again serve distinct attentional sensory motor goals. Lesions in the posterior parietal cortex disrupt the egocentric spatial frame whereas lesions in the frontal lobe disrupt allocentric spatial frames.

TBI

Definition

The complexity of the visual system makes its anatomical and functional connectivity vulnerable to TBI. Many of the tracts are long, and some are quite small and delicate, particularly those in the brain stem. TBI is a neurobiological process affecting the brain by physical forces. When a TBI occurs, the cerebral hemispheres move back and forth, pivoting around the upper brain stem. Some of the brain structures are partially secured, such as the cerebellar hemispheres by the tentorium, and the cerebral hemispheres by the falx, diminishing side-to-side movement. Because of the contour of the skull and the way the brain sits in it, the most common areas of contusions occur in the ventral and anterior frontal lobes and the anterior tip and lateral frontal portions of the temporal lobes as they abut upon the jagged edges of the anterior and middle facet of the cranium (see Figure 9.11a and 9.11b).

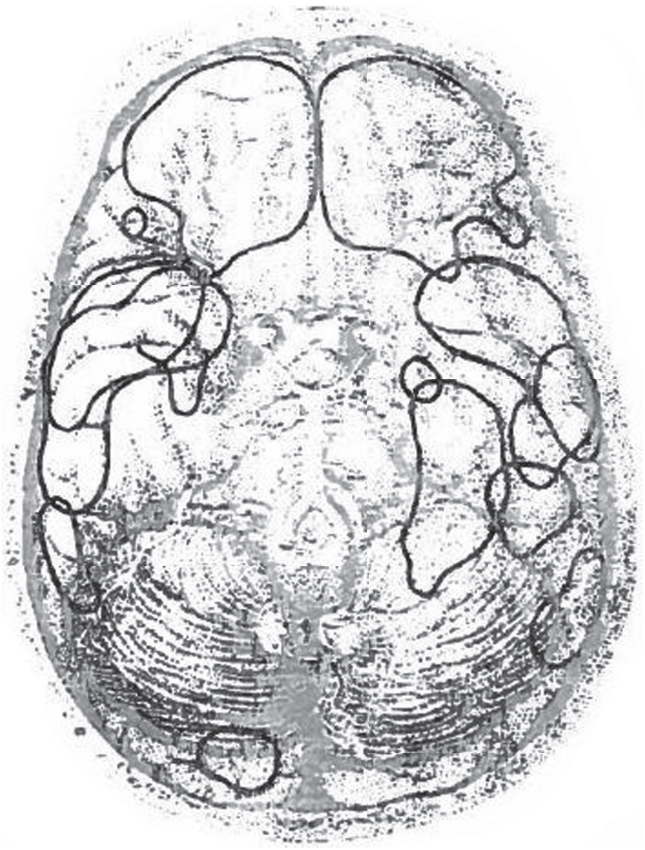
Primary effect

Cranial cerebral trauma can be divided according to the injury to the skull. Closed head injuries are those in which the skull remains intact and can include the presence of a nondisplaced linear skull fracture. A closed head injury can also occur without a direct physical force to the skull, such as with a neck injury, particularly when the head is unsupported. An open head injury is diagnosed when a fragment of bone depresses upon or injures the underlying brain tissue. This includes blunt trauma to the skull or with an object such as a bullet. As noted with closed head injuries, additional inertial forces can result outside the areas directly impacted, resulting in bleeding and sheering injuries. The intensity of the force and the movement of the head determine the severity of the injury. Focal types of brain injuries can include contusions and bleeding. Contusions occur primarily in the cortical tissues as these are most superficial. They typically form a wedge shape with the widest part in the outermost part of the brain. Like bruises in other tissues, cerebral contusions are associated with cellular dysfunction and blood vessel damage, resulting in either microbleeding or a large area of hemorrhage and edema. Cerebral microhemorrhages are seen predominately in the white matter. The large areas of intracranial bleeding are located either extracranially or intracranially. Those located extra-axially are called either subdural or epidural hemorrhages whereas intra-axial bleeding is termed intracerebral hemorrhage. The intracerebral hemorrhages are typically located in the cortical or subcortical areas. Subarachnoid hemorrhages result from blood vessel damage in the subarachnoid space. A diffuse axonal injury (DAI) is a specific type of brain injury describing the stretching and torsional forces of the white matter or the axonal tracts. This results in disruption or loss of axonal cytoskeletal integrity, demyelination, interference of transmission of electrical impulses, and loss of axonal energy supply.

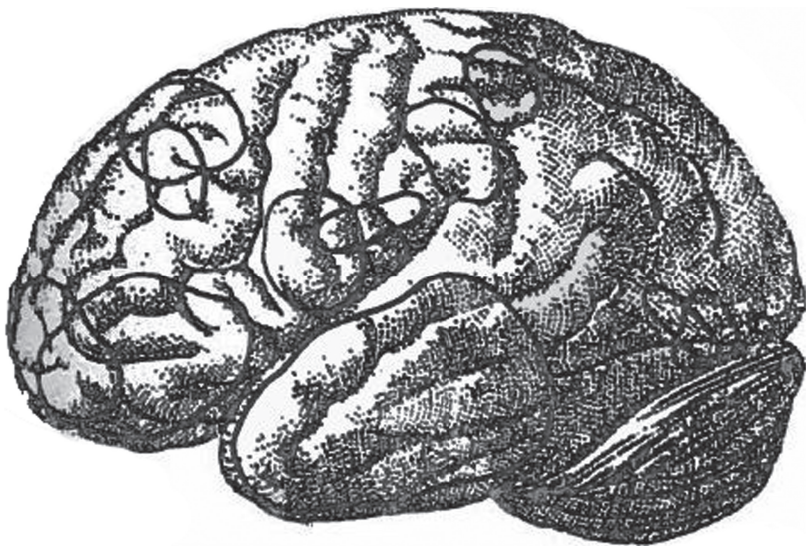
The rostral brain stem and midline structures are most vulnerable to DAI. The midline structures include the long association tracts and those commissures interconnecting the hemispheres, most prominently the corpus callosum. Collectively, these constitute the primary changes occurring with TBI and can be seen in the majority of imaging studies, especially MRI with DTI.

Secondary effects

However, following the initial injury, secondary changes are set in motion, resulting in metabolic derangement and altering cell function and connectivity. This is the basis for the traumatic chemical cascade as described by Hovda.[32] The normal adult brain is only 2% of body weight but consumes 20% of body energy. The neuron has virtually no ability to store energy. It is highly dependent on aerobic metabolism of glucose to generate ATP. TBI is a major "stressor" to the brain, causing both physical and metabolic changes in cell function. There is initial depolarization on neurons,



(a)



(b)

Figure 9.11 **(a)** Lateral view of the human brain. The circled areas represent potential areas of cortical injury in minor head injury syndrome. **(b)** The base of the human brain. The circled areas indicate potential areas of cortical injury in minor head injury syndrome. (With kind permission from Springer Science+Business Media: *Minor Head Trauma: Assessment, Management, and Rehabilitation*, 1993, pp. 7–8, S. Mandel, R. T. Sataloff, and S. R. Schapiro (eds.).)

causing release of the excitatory neurotransmitter glutamate, and ionic shifts in cell membranes, all of which results in changes in cell signaling. There is an initial increase in energy demand associated with decreased initial blood flow, creating an energy crisis, further compromising neuronal function and axonal connectivity. This same process occurs in mild, moderate, or severe TBI with its duration determining outcome. The end result of this process is dependent upon the nature of the injury, medical complications, treatment received, and epigenetic factors. Microglial activation occurs to combat "stress" with an inflammatory response to restore and regain function.

In some cases and especially with repeated TBI, the immune system's anti-inflammatory response can convert to a proinflammatory response and sets in motion a possible neurodegenerative state. Bigler's article is one of many articles showing evidence of progressive brain loss following TBI.[33] Recent evidence indicates that not only repetitive TBI can be a risk factor for the development of dementia,[34] but also head trauma by itself is the single strongest environmental factor consistently associated with the further risk of neurodegenerative states such as Alzheimer's disease[35] and Parkinson's disease.[36] TBI not only disrupts the visual anatomic functional connectivity (gray/white matter) but input to other neural networks.

CLASSIFICATIONS OF VISUAL DEFICIT

Considering 50% of the brain is involved in visual function, it is not surprising that visual problems are one of the most common complaints after TBI. The visual deficits are discussed in relationship to the functional system disrupted, those being the receptive, attention, and higher processing systems.

Receptive system

The purpose of reception is to provide the most accurate visual representation to the PVC for advanced processing as to the "what," "where," and "how" systems for visual cognition. The receptive system consists of the optical system, the oculomotor system, and the primary visual system. The optical system is not commonly directly impacted in TBI; however, it is frequently indirectly altered by damage to the oculomotor system thereby impacting bilateral foveation. Because the infranuclear portion of the gaze system is in the rostral brain stem, it is very vulnerable to DAI. This can involve the axonal projections of cranial nerves III, IV, and VI as well as their nuclei. The function of the oculomotor nerve complex is frequently involved. Disruption of this complex results in an abnormal accommodation reflex, that being accommodation, convergence, and miosis. This results in convergence insufficiency, high exotropia and exophoria, and accommodation dysfunction, resulting in visual spatial dysfunction. This is called posttraumatic visual syndrome. There is a loss of bilateral foveation with complaints of diplopia, blurred or hazy vision, dizziness, eye strain, problems reading, and motoric integration with the environment. Ciuffreda found in a large study of patients with TBI that the overall occurrence of oculomotor dysfunction was 90%, and the nonacquired brain injury asymptomatic sampling was 20%.[37]

The supranuclear portion of the oculomotor system is less commonly involved in TBI and, when present, usually is secondary to a contusion to the general area of the frontal eye fields or its connections. This results in horizontal gaze palsy. Horizontal and vertical gaze palsy can result in brain stem lesions, but in those conditions, there is usually a plethora of other brain stem neurological abnormalities on exam. Disorders of the primary visual system, the retinogeniculocortical tract, results in scotoma or visual field defect. A scotoma is defined as an area of partial attenuation or loss of visual acuity surrounded by an area of normal preserved vision. Lesions in the optic nerve cause monocular scotoma, the shape of which is dependent upon which nerve fibers are involved. Lesions of the optic chiasm usually result in a bitemporal hemianopsia or blindness in the temporal half of both visual fields. Retrochiasmal lesions cause contralateral hemianopsia, which is blindness in one half of the visual field. Lesions in the optic tract produce incongruous visual field defects because the fibers from each eye are still not adjacent to each other. Posterior optic radiation lesions result in homonymous quadranopsias, primary visual cortex lesions sparing the posterior portion result in macular sparing homonymous hemianopsias, and total bilateral primary visual cortex lesions cause bilateral homonymous hemianopsias.

Attention system

Once the brain receives the visual representation, it can then attend to it in that hemispace. Disorders of attention vary in regards to the network involved, i.e., the attention arousing, orienting, or selective attentional network. The reticular activating input to the thalamus and cortex is necessary to be awake and for conscious awareness. Disruptions in the reticulofrontal pathway result in decreased attention and impaired speed of processing. This system is fundamental for all cognition, essentially serving as an "ignition switch." The orientation network is responsible for preattention or the screening or selecting out of irrelevant signals as there are limits of the brain's attentional capacity. This is an automatic subconscious process carried out primarily in the pulvinar. Blindsight is an example of the subconscious ability to orient to visual stimuli. In patients with a unilateral occipital lesion who demonstrate a contralateral homonymous hemianopsia, they are still able to subconsciously discriminate some form, color, or orientation in that hemifield. The selective attentional system is a cortical system preparing for the conscious visual awareness picking out relevant information from distractors in vision. The disruption of this system results in visual hemispatial neglect, a disorder of higher visual processing.

Higher visual processing system

The last area of classification is that of disorders of higher visual processing. Although an oversimplification, the easiest approach to conceptualize disorders of higher visual perceptual and visual spatial processing is to think of disconnections in either the ventral or dorsal streams. Disconnections involving the ventral stream can be classified as visual/visual, visual/verbal, or visual/limbic. Visual/visual disconnections result in agnosia. Agnosia refers to the clinical condition in which the patient is able to perceive visual stimuli and has preserved language capacity to name the visual representation but recognition is lost. These conditions include the loss of recognition of object features, object identity, faces, places, and color. These conditions are named, respectively, visual apperceptive, visual associative agnosia, prosopagnosia, topographagnosia, and color agnosia. Apperceptive visual agnosia is the condition in which the patient cannot distinguish one form from another whereas visual associative agnosia is the disturbance of visual recognition with intact visual perception. Loss of connectivity between visual/verbal systems results in pure alexia, color anomia, and object anomia. Visual anomia indicates recognition is intact but the ability to name the entity is impaired. Impaired linkages between visual/limbic areas result in visual amnesia and hypoemotionality with the latter including the inability to recognize facial expressions.

Disorders in the dorsal stream result in malfunction in the "where" or "how" system. Impaired connectivity with V5 results in the abnormal analysis of optic flow and a loss of motor perception called akinetopsia. Visual spatial processing disorders occur when there is a disconnect between the dorsal stream and the spatial representation resulting in contralateral visual hemineglect. Optic ataxia or misreaching to a visualized target is a visuomotor disconnect with which retinotopic representations fail to convert into craniotopic representations. One of the most devastating clinical neurological conditions is Balint–Holmes syndrome.[15] This results from bilateral occipitoparietal lesions, causing bilateral visual spatial neglect. Components of this syndrome include bilateral visual inattention or simultanagnosia, which is the inability to attend to more than one object at a time. Two other components include optic ataxia and acquired oculomotor apraxia. A fourth component is a disorder of spatial representations. This functional component is an impairment of spatial relations with patients misjudging distances and the size of objects. In essence, the patient functions as a blind person with a broad-based gait, arms outstretched and bumping into objects. The patient's visual field is only a spotlight of vision that fades in and out as the patient or objects move in the environment.

Accurate visual-perceptual and visual-spatial processing impacts not only vision but also its input to other cognitive domains. The other domains include attention, language, memory, and executive function. The visual attentional connections have already been discussed. Visual representations in both the ventral and dorsal stream are initially coded in the hippocampus and then stored in nearby visual association areas from where they were initially processed. They are retrieved and interwoven with language function. Visual mental imagery is a crucial cognitive function. Mental imagery relies on similar cortical and subcortical systems that are used during perception of environmental stimuli. The visual, verbal, and semantic memories are stored in the posterior portion of the brain in the temporal, parietal, and occipital lobes. This is descriptive knowledge or how things are.[38] Prescriptive knowledge is localized in the prefrontal cortex in the anterior association area. This is how things should be and what must be done to set things according to our wishes and our needs.[38] This consists of complex patterns of memory that are used for executive and cognitive social function. The attentional system binds these together with the limbic system to add motivation and emotion to our decision making. Vision is also important for social cognition. Vision is key to social signaling for body gesture, position, and interpreting facial expression and directs our social interaction, which requires planning, evaluation, self-control, empathy, and theory of mind. The social network, the prefrontal cortex, amygdala, insula and anterior cingulate, and their connections are located in the anterofrontal and temporal areas. This network is susceptible to TBI, including damage to both its white and gray matter components, resulting in emotional and cognitive deficits commonly seen following TBI.

SUMMARY

The function of vision occupies vast areas of cortical and subcortical cerebral structures and is supported by an immensely complicated neurological and neurophysiological system. Anatomic and functional connectivity are integral to the ability of vision to support motor, communicative, emotive, and cognitive functions. TBI can, and often does, disrupt one or more aspects of the visual system. Clinical observation and diagnostic undertakings for individuals with TBI should carefully consider the role of disruptions to aspects of the visual system. In order to do so effectively, a firm understanding of the anatomy and functional connectivity of the visual system is necessary. Interventions are available for many, although not all, dysfunctions that can arise from an injury and should be undertaken within the context of a comprehensive rehabilitation program.

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Potential utility of resting state fMRI–determined functional connectivity to guide neurorehabilitation

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INTRODUCTION

Literature is replete with functional magnetic resonance imaging (fMRI) studies of brain function showing useful correlates to behavioral outcome in many central nervous system (CNS) disease states. However, far less has been achieved within the neurorehabilitation field, and we posit that resting state fMRI (rsfMRI) techniques could be eminently useful for determining the impact of current neurorehabilitation techniques as well as optimizing and establishing new methods to improve outcome after traumatic brain injury (TBI). In this review, we set out to describe a number of studies that show the sensitivity of rsfMRI to altered brain function after injury as well as the potential for following plastic changes within the brain as a way of improving our understanding of how current rehabilitation methods may be followed and improved upon using feedback from neuroimaging data obtained concurrently.

DETERMINATION OF FUNCTIONAL CONNECTIVITY WITH rsfMRI

Since the very first rsfMRI study that showed a high degree of temporal concordance between spatially varying blood-oxygen-level dependent (BOLD) signals in motor cortex regions well known to be connected,[1] there has been an explosion of interest in examining BOLD signals collected during scans at rest using the so-called rsfMRI protocols. Although it is known that neuronal-based local field potentials underlie task-evoked BOLD response,[2] the physiologic correlate of the temporally varying BOLD fluctuations is still largely unknown. Several studies conducting simultaneous electroencephalographic (EEG) and rsfMRI have shown good correlations among multiple frequency bands[3,4] supporting the now widely accepted neuronal origin of the signal. It is the temporal covariance of the BOLD signal across and within brain regions that is used to describe individual brain networks or spatially oriented neuronal circuits that show temporally concordant activity and are presumed to be functionally integrated networks of cells. It is this coupling of BOLD or indirect neuronal activity that is used to describe regions of brain that are likely to show functional connectivity (FC).

METHODS USED TO DETERMINE NETWORK FC

There are currently three major methods that are commonly used to analyze the raw rsfMRI signal in order to obtain the different network components of the brain. The simplest form is the seed-based, region of interest (ROI) approach, which enables the interrogation of the brain based on a priori information, either from an anatomical basis (a brain anatomical or functional atlas) or from other data sources pertinent to the understanding of the experiment being conducted. Independent component analysis

is a data-driven, model-free approach that has been used to delineate regions of spatially contiguous function based on the underlying temporal BOLD signal fluctuations, for example.[5,6] Finally, graph theory analysis is a mathematical network-based method that has gained application in this field. It provides a more fine-grained approach that combines the benefits of the unbiased nature of ICA with the specificity of the ROI approach of the seed analysis in order to construct the brain connectome, or connectivity-based graph, which is then analyzed by a set of algorithms used to quantitatively describe the network architecture.[7] Other approaches are composed of multivariate pattern classification analysis and various clustering algorithms.

MAJOR BRAIN NETWORKS

The integrated action of widespread, distributed networks within the brain is critical for cognitive functioning.[8] Both the connections between brain regions within a network as well as those connections between discrete networks comprise fundamental physiologic foundations of cognition.[9,10] An overwhelming number of brain networks have been discovered utilizing rsfMRI methods. The focus of this chapter is on the more extensive neural networks that connect remote brain regions referred to as intrinsic connectivity networks (ICNs; Figure 10.1).[11] Some core ICNs include the default mode network (DMN), salience network (SN), attentional network, visual network, sensorimotor network, and frontoparietal control network (FPCN). Synchrony and efficient interaction among these networks allows for successful cognition (i.e., memory and attention). It follows that TBI may disrupt the ICNs and result in impairments in cognitive function.

The DMN is the most highly studied network, and the predominant centers of connectivity within this network are located in the ventromedial prefrontal cortex, posterior cingulate cortex/retrosplenial cortex, medial temporal, and precuneus areas/regions.[10,12–14] The DMN network is highly activated at rest and deactivated when cognitive effort is required.[13] The DMN functions on a continuum wherein the amount/degree of activation/deactivation is dependent on the amount of cognitive effort. Abnormal activity in the DMN has been noted in TBI patients.[15] Following a TBI, activation of the DMN has been observed to increase in the injured versus the noninjured brain during cognitively taxing tasks.[15] This may be due to a greater cognitive effort required to accurately complete a cognitive task. In a study that examined both FC at rest and during a choice reaction time task, there was a correlation between FC of the ventromedial prefrontal cortex and evoked brain activation.[16] These findings would suggest that following TBI, high "resting" DMN functional connectivity is associated with greater processing speed. Sustained DMN resting connectivity changes may affect behavior by influencing the

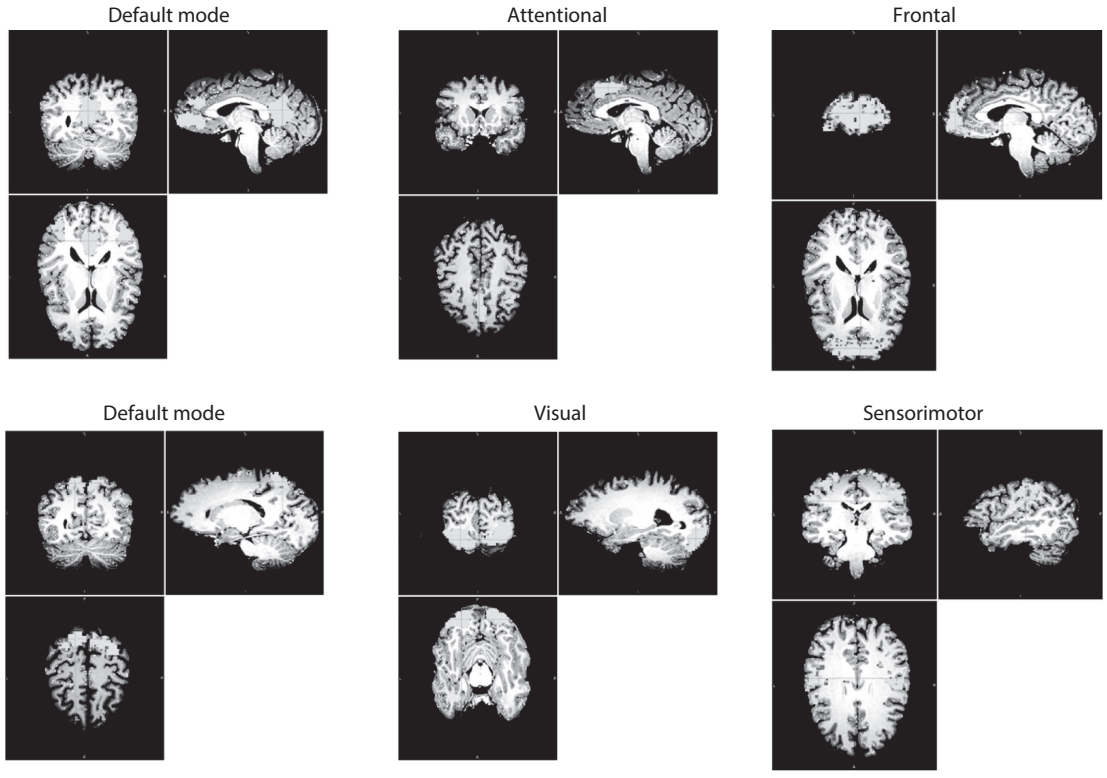

Figure 10.1 **(See color insert.)** Examples of some of the major functional brain intrinsic connectivity networks identified from a single volunteer using resting state fMRI data acquired at 3Tesla. Independent component analysis was used to compute the major network components using the Gift toolbox. (From Guo, Y., and Pagnoni, G., *NeuroImage*, 42: 1078–93, 2008.)

responsiveness of other networks utilized during specific tasks.[16] The relative activation level of the DMN has been shown to be associated with outcome in TBI in another fashion. A failure to deactivate the DMN following TBI has been also been associated with cognitive impairments and was attributed to inefficient inhibitory control mechanisms.[15] Finally, altered interactions between networks due to TBI-induced structural damage on one network have cognitive consequences. Underlying damage to tracts within the SN has been shown to be correlated with reduced FC to the DMN and reduced cognitive control.[17]

Although the DMN is a so-called "task-negative" ICN, in that it becomes inactive during attentional or other task-based effort, the frontoparietal control network (FPCN) is referred to as a task-positive network.[18] This means that the FPCN is activated when direct attention is required. This network includes areas in the anterior and dorsolateral prefrontal cortex, the anterior cingulate cortex, the anterior insula, and the anterior inferior parietal lobe.[18] Increased activation in regions of the FPCN during cognitively taxing exercises has been observed in patients following TBI.[19,20]

The SN overlaps with regions of FPCN and includes paralimbic structures, such as the dorsal anterior cingulate and orbital frontal insula with connections to subcortical and limbic structures.[21] This network is thought to interact with other networks when a change in behavior is necessary. For example, in the case of motor control, the SN interfaces with the DMN by causing an increase in FC concomitantly with rapid change or inhibition of motor responses.[17] This increase is not observed in TBI patients with poor motor control, which indicates that the SN may be a necessary constituent of efficient control of DMN activity when a rapid change in behavior is required as a result of a change in the environment.[17]

POTENTIAL PHYSIOLOGIC CORRELATES OF ALTERED FC

An increasing number of rsfMRI FC-based studies report FC deficits after mild, moderate, and severe TBI, for example,[22–24] and this is presumed to occur due to either frank tissue loss after contusion injury, associated structural/axonal disconnection, or even indirect functional disconnection of remotely connected areas, so-called diaschisis. Persistent reductions in posterior cingulate cortex connectivity (part of the DMN) among patients 6 months to 6 years postinjury were related to the degree of white matter damage in the corpus callosum.[16] This indicates that altered structure might be driving the functional deficits in agreement with others.[25] However, no such agreement was shown in a combined fiber tractography and task-based rsfMRI study.[26] In fact, the exact morphologic and/or physiologic substrate that underpins the reductions in FC are still unknown. It might well be a compendium of all these processes as well as, or alternatively, more subtle alterations, such as synaptic density changes, receptive field size alterations, or simply changes in the balance of excitation–inhibition underpinned by receptor modifications. One set of observations that make the latter, subtler mechanisms more plausible is the measured regional hyperconnectivity after both clinical[23,24,27] and experimental TBI.[28] The presence of hyperconnected regions is presumed to indicate functional compensation, and if correct, this would suggest that the up/down alterations in FC may not simply be a reflection of altered structure as occurs in healthy normal brains[29] but the result of a far more complex alteration between a compendium of physiologic parameters.

CURRENT EVIDENCE FOR FC AS AN OUTCOME MEASURE FOR INJURY AND REHABILITATION

Clinically, early improvement of most cognitive function occurs at a fast pace in many individuals at 2–5 months after injury; thereafter the recovery rate slows at 5–12 months.[30] An acute postinjury neuroimaging study found significant increases in FC between 3 and 6 months after severe TBI,[31] which may well represent the neurologic substrate of the early recovery period. The same work showed that although there was also functional disconnection within networks involved in goal-directed behavior in regions of dorsolateral prefrontal cortex and anterior cingulate cortex, increased connectivity occurred in medial prefrontal and posterior cingulate cortex, regions commonly associated with self-reflection or internal states.[32] Thus, it would seem that although neurologic recovery can be monitored with rsfMRI, the network pattern of connectivity may not simply be a compensatory upregulation of novel regions normally not associated with lost function, but it may involve a complex set of a spatial and temporal sequence of new connections and disconnections that comodulate to promote behavioral recovery.

Unlike most other brain functional domains after TBI, motor, visuospatial, and visual memory function continue to show recovery at 5–12 months after moderate to severe injury.[30] Motor areas are one of a number of brain regions that show hyperconnectivity in conjunction with the DMN circuit even 2–10 months after mild TBI.[33] What this response relates to is unknown, but others have found a robust decrease in the hyperconnectedness of the posterior cingulate cortex contribution to the DMN circuit from the subacute to chronic postinjury stages.[34] It is, thus, tempting to consider that the period of hyperconnectivity reflects a temporary state in which the brain is connectively promiscuous and inherently plastic, beyond which the brain is less malleable from neurorehabilitative intervention. For the moment, however, this remains a speculation. Some similarities do exist within morphologic data from animal injury models. Cortical dendritic density increases acutely in the homotopic cortex opposite injury to the forelimb brain area,[35] that is driven by a use-dependent effect from the unimpaired limb,[36] which is then followed by a chronic phase of dendritic pruning.[37] Although it is unknown whether dendritic arborization directly relates to

FC measured by rsfMRI, it will be useful for future clinical studies assessing motor injury function post-TBI to determine whether the same temporal association exists between FC and behavioral outcome in regions homotopic to the major sites of injury. Given the potential importance of the contralateral hemisphere to recovery of function experimentally after stroke[38] and TBI,[39] studies designed to monitor rehabilitation through rsfMRI should be able to begin to disentangle whether the less severely injured hemisphere should be treated differently from the more severely injured one after brain injury.[40]

As far as the predictive potential of rsfMRI data, there is good evidence that when it is acquired acutely postinjury, it is sensitive to the degree of predicted cognitive deficit.[23,41] FC data also exhibits good correlation to both attentional performance at subacute and acute stages within the DMN[42] as well as to performance on a neuropsychological test measuring organizational skills and visuospatial abilities within the frontal-parietal network.[43]

However, clearly not all individuals will recover at the same rate or at all, and some will worsen so that it will also be important for further studies to improve accuracy for determining the association between altered patterns of connectivity and specific types of behaviors that are associated with recovery or persistent dysfunction. This will improve the potential clinical utility of rsfMRI as a valuable prognostic tool and as a clinical monitoring utility that may well be used at the level of a single patient as part of a patient-tailored approach proposed for structural imaging.[44]

FUNCTIONALLY GUIDED REHABILITATION—THE FUTURE?

There remains much that we do not know about rehabilitative intervention post-TBI. This includes knowledge of the optimum time postinjury to begin the intervention, the duration of treatment, and the most effective protocols to provide the best functional outcome. Although tools such as the Functional Independence Measurements,[45,46] the Mayo Portland Adaptability Inventory,[47] Independent Living Scale,[48] and the Disability Rating Scale[49] have historically been the absolute yardstick by which to measure patient outcomes following injury and subsequent rehabilitation, rsfMRI may well provide an additional, more sensitive measure with which to accurately diagnose deficits in brain circuitry underlying TBI-related behavioral symptoms and as a tool with which to guide and monitor the direct effect of rehabilitation on brain network connectedness in order to improve outcome.

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11

TBI and sensory sensitivity: Translational opportunities

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INTRODUCTION

Traumatic brain injury (TBI) is a central nervous system injury that occurs as a result of mechanical force being applied to the body or cranium that is transmitted to the brain and its associated structures.[1] Each single event, by definition, occurs in milliseconds and initiates subsequent physiological and cellular processes. The primary injury event directly, possibly irreparably, damages neurological and vascular tissue. It follows that direct damage may go on to trigger subsequent processes of cellular pathophysiology, referred to as the secondary injury cascade.[2] This cascade disrupts physiological processes through cerebral edema, ischemia, hypotension, and metabolic challenges.[3–6] At a cellular level, excitatory amino acids and platelet-activating factors disturb ion channel conductance, ultimately impacting tissue homeostasis and exacerbating metabolic failure.[7] These cellular processes are self-perpetuating, often exacerbating damage, whereby pharmacological intervention could improve outcome by controlling damage.[2] In the presence or absence of treatment, injury-induced deficits in neurological function (e.g., dizziness, headache, amnesia) likely occur, which can recover, persist, or transition into morbidities over time.

Previously, TBI largely had been considered a singular event, but the longitudinal neurological consequences have been recognized as part of a chronic disease process more recently.[8] Long-term neurological symptoms originate from injury-related pathological processes that dismantle and then go on to impair brain circuit function and activation. In response, restorative and regenerative processes may not faithfully resurrect the brain to preinjury architecture, leaving reorganized circuits prone to sensory sensitivities, seizure, motor deficits, sleep disorders, neurodegenerative disease, neuroendocrine dysregulation, and behavioral changes.[8–10] In this way, TBI can be classified as a disease and chronic disorder of the nervous system. An estimated 43% of Americans experience long-term complications following a single TBI event.[11]

Survivors of brain injury face a lifetime of potential cognitive, emotional, and somatic consequences of their injuries. Enduring cognitive morbidities include delayed mental processing, lack of concentration, and learning or memory deficits that adversely affect activities of daily living.[12–14] A gamut of psychiatric and emotional disorders arise as well, leaving people with varying levels of depression, anxiety, posttraumatic stress disorder, and addiction. In a cohort of military personnel, upward of 40% of TBIs sustained during combat resulted in persistent somatic changes including a sensitivity to light (photophobia) and noise (hyperacusis).[15] In this chapter, we focus on the somatic consequences of injury, which include postinjury photophobia and hyperacusis. The underlying somatic circuits avail themselves to investigation of the pathophysiological consequences, functional measurements, and rehabilitation therapy.

VISUAL SENSITIVITY

Given the volume of neural tissue that subserves vision, reduction in visual performance is understandable following TBI. The complexity of vision involves oculomotor coordination for conjugate gaze (controlled by brain stem cranial nerves) through image processing for feature detection (higher cortical regions). All of the complex visual functions are susceptible to the primary and secondary injuries after a TBI event; here, we briefly discuss sensitivity

to light. Photophobia is a broad term defined as an abnormal sensitivity to light[16] and is a common symptom patients experience throughout recovery from all severities of TBI. Light sensitivity can affect the patient immediately—"seeing stars"—and can increase in severity in the days following injury and enduring for up to 6 months or longer.[17] Considering that light sensitivity is a sensory feature, rather than motor, the painful stimulus arises in the eyes, and propagates through the retina and optic nerve.

A frontal force (e.g., helmet-to-helmet collision) may initiate light sensitivity via anterior–posterior translation of the brain, resulting in coup–countercoup impact on the occipital lobe.[18] Impact-derived neuronal damage, in terms of diffuse shearing or tearing of axons, leave components of the visual system metabolically disrupted altering function.[2] As the visual circuit recovers, the circuit can reorganize to alter the magno–parvo system equilibrium and downstream thalamo-cortical tracts, leading to increased light sensitivity and postconcussive vertigo.[19] The magnocellular subsystem, responsible for rod receptor function and dim light sensitivity, may be particularly susceptible to TBI. Damage to this system disinhibits the parvo system and the cone receptors, which are responsible for bright light sensation. Without rod reciprocal inhibition, light stimulus overloads the neuronal circuitry leading to a painful response.[19]

At a cellular level, reactive synaptic connections are being formed at multiple junctions in the neural circuitry, adding unnecessary complexity to information processing, hampering efficiency, and increasing the system's sensitivity to light stimuli. With light stimuli, signals can diverge with an amplified intensity throughout the brain. We propose that both the location and the magnitude of the signals contribute to the subjective experience of light sensitivity and photophobia. Contemporary studies on postconcussion syndrome could be evaluated with fMRI, using bright light stimuli to activate (or overactivate) visual pathways, thereby expounding an anatomical basis for the patient's physiological responses.

AUDITORY SENSITIVITY

Following TBI, sound sensitivity (hyperacusis), similar to light sensitivity, is an important and underappreciated symptom that can arise through several mechanisms. Following an impact to the head (or a blast-related noise), pressure waves propagate through the skull disrupting vascular supply and cochlear hair cells responsible for auditory and vestibular sensation. Damage to the hair cells elicits and exacerbates posttraumatic tinnitus (e.g., ringing), vertigo, nausea, and ataxia.[20] Cochlear and vestibular labyrinth fluid volume and chemical composition are disturbed, disrupting underlying circuitry, with the potential for subsequent circuit reorganization.[21] The facial nerve (cranial nerve VII) is also implicated in hyperacusis and auditory dysfunction following TBI, primarily in the attenuation of sound intensity via the stapedial reflex. The nerve lies just outside the external acoustic meatus on the lateral surface of the head, making it vulnerable to lateral impacts (e.g., a punch to the temple). Mechanical damage or aberrant recovery following TBI could disrupt the reflex resulting in an inability to regulate sensory information propagating to the auditory cortex.[22]

The acute loss of auditory sensory function can limit or prevent language processing and comprehension with substantial impact on quality of life for TBI survivors. In the more chronic disease process, trauma and persistent inflammation within the inner ear can limit sound transduction; however, the extent of damage is difficult to discern. fMRI techniques with white noise or pure-tone stimuli can distinguish and identify the extent of conductive or sensorineural auditory dysfunction. Neural reorganization and collateral sprouting from injured nerve fibers within auditory circuitry generate tone deafness, disrupting overall sensory stimuli processing. Misinformation can arise from elevated background noise masking the true auditory signal, leaving the individual with an overwhelming cacophony of auditory information that could be interpreted as painful. The same stimuli can induce sound-triggered autonomic hyperexcitability while inappropriately activating affective brain regions (amygdala and hippocampus), thereby generating complex comorbidities, such as auditory associated posttraumatic stress, anxiety, and fear.[23] The constellation of damage to vision (served by cranial nerves II, III, IV, and VI) and audition (served by cranial nerves VIII and VII) bring into play somatic comorbidities, if not primary morbidities, that can exacerbate cognitive and affective symptoms, ultimately degrading quality of life.

EXPERIMENTAL APPROACHES

Various experimental models have been employed to investigate the specific markers and pathophysiology of hypersensitivities following TBI. Sensory sensitivities have the advantage of being anatomically delineated circuits with defined functions. For the rodent, the whisker circuit subsumes a significant portion of the neural tissue to process information from the facial whiskers about size, shape, and texture of objects and the environment.[24–26] This information is used in tactile exploration and communication. As a purely glutamatergic circuit from the brain stem, through the thalamus, into the cortex,[27,28] it serves as a unique model for in vivo circuit disruption that can be monitored over time for structural and functional changes in the development of persistent sensory sensitivity after TBI in rodents. Several laboratories have adopted the whisker nuisance task (WNT) to evaluate sensory sensitivity[29–32] with the translational application toward light and sound hypersensitivity discussed previously in brain injury survivors.

The WNT evaluates the rodents' response to whisker stimulation by a wooden applicator stick with higher scores representing freezing; defensive and fearful movements, such as cowering; grounding posture; forced or

gasping breathing pattern; reduced movement of the whiskers; escape or avoidance behaviors; vocalization or aggression; or anxiety directed toward the stimulation (stick).[25] Uninjured rodents are curious or ambivalent during the WNT.

Ongoing investigations indicate that sensory sensitivity arises from structural changes in the whisker circuit as the pathophysiology of brain injury progresses. In response to injury, cellular damage includes axotomy and synaptic deafferentation.[33–35] Posttraumatic deafferentation is then followed by responsive neuroplastic changes in surviving (albeit atrophied) synaptic terminals.[36] However, these uncoordinated neuroplastic changes do not faithfully recapitulate the preinjury neural circuitry, thereby giving rise to neurological dysfunction. In the situation of the whisker circuit, neurological dysfunction results from morphological changes to somatosensory thalamic neurons and hypersensitive presynaptic glutamate release.[25,37] The distributed reorganization is evidenced by brain injury survivors exhibiting broad and widespread patterns of neural activation compared to control subjects when functionally imaged during cognitive tasks[38,39] or rest.[40]

TREATMENTS

Clinical treatment for sensory sensitivities after TBI are limited to the extent that they exist at all. Randomized, controlled clinical trials are absent, and only a few case studies have been published. Current medical management guidelines suggest directly treating the sensory sensitivity, similar to a patient presenting with an idiopathic hypersensitivity, or developing compensatory strategies. In these cases, tinted lenses or earplugs can be used acutely to mitigate photophobia and hyperacusis, respectively.[41] Some indications are available that sensory sensitivity can subside while physical mitigation approaches are in place. Pharmacological interventions are an available treatment option, which include barbiturates (sedatives) to improve sleep, reduce nerve pain, and the unpleasant effects of sensory sensitivity.[42] Beta-blockers, calcium channel blockers, anticonvulsants, and gabapentin can prophylactically treat headaches arising from persistent sensory stimulation.[43] Antidepressants can alleviate hypersensitivity symptoms concomitant to treating underlying disorders. For example, selective serotonin reuptake inhibitors treat hypersensitivities and comorbid disorders, such as migraine, depression, and posttraumatic stress disorder.[44,45] With comorbid depression, antidepressants, such as levodopa, can alleviate TBI hypersensitivity, similar to antianxiolytics in patients with anxiety disorder.[46,47] A select few nonpharmaceutical procedural treatments have reduced photophobia symptoms, such as injections of botulinum toxin into the supraorbital nerve or orbit to reduce pain and inflammation.[42] Cognitive behavioral therapy desensitization has been successful in treating hypersensitivities; however, a substantial proportion of TBI patients with sensory sensitivity are unable to find relief, relying on the eventual, natural improvement of symptoms over time.[48]

In the laboratory, pharmacological and rehabilitative approaches are evaluated for therapeutic efficacy. Direct whisker rehabilitation and exposure to complex environments both are intended to activate whisker circuits[49] and hold the potential to alleviate or prevent posttraumatic sensory sensitivity. These interventional approaches are designed with consideration for physical medicine and rehabilitation interventions that promote adaptive plasticity. Pharmacological approaches continue to target all elements of the neurovascular unit, including synapse formation to prevent maladaptive plasticity and promote adaptive reorganization. Future studies can combine the physical and pharmacological approaches to augment recovery.

CONCLUSION

Posttraumatic sensory sensitivities are somatic morbidities that include photophobia and hyperacusis, which can expand into vertigo, dizziness, and facial nerve pain. These persistent neurological symptoms contribute substantially to disability and decrease quality of life after TBI[50–52] even of mild severity. The evaluation, management, and eventual treatment of sensory sensitivities resulting from TBI largely follow treatment courses for idiopathic or primary hypersensitivities found in the absence of TBI. In the case of TBI, it remains important to recognize the origin and ensuing pathophysiology of the somatic symptoms where the initial TBI event leads to circuit dismantling, where reorganizes during the disease process to elicit somatic neurological symptoms. In essence, injured, but repaired, circuits remain after diffuse brain injury to form the anatomical substrates for neurological dysfunction.

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12

The neuroimaging challenges in hemispherectomy patients

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INTRODUCTION

Hemispherectomy (more recently referred to as hemispherotomy or callosotomy) is a complex surgical technique designed to disconnect one cerebral hemisphere from the other. Originally utilized in the 1920s to treat gliomas, hemispherectomy techniques have been refined considerably since then. Modern hemispherectomy procedures have been used to effectively treat intractable epileptic seizures, and multiple different techniques have been used to achieve cerebral resectioning, including anatomical hemispherectomy, functional hemispherectomy, and current hemispherotomy techniques. These methods are characterized by the amount of brain tissue physically removed: Anatomical hemispherectomy refers to the near-total excision of a cerebral hemisphere, functional hemispherectomy is more precise in that the majority of the affected hemisphere is functionally disconnected but left physically intact, and hemispherotomy specifically targets the corpus callosum such that minimal brain matter is excised. Four common goals have been consistently recognized throughout the history of the procedure as necessary for a successful hemispherectomy surgery: the internal disruption of the internal capsule and corona radiata, resection of the medial temporal structures, transventricular corpus callosotomy, and disruption of the frontal horizontal fibers.

HISTORY

Hemispherectomy has been used as a surgical technique since the early twentieth century, when Dr. Walter Dandy removed gliomas from five patients in 1928 with relative success.[1] He employed a technique known as "anatomic hemispherectomy," whereby a large portion or the entirety of a cerebral hemisphere is removed from a patient. The process involved the immediate elimination of cerebral blood supply followed by ligation of veins entering sinuses, achieved by either snipping the veins at their point of entrance into the sinuses or suturing them in the cortex. Following this, hemispheric connections to the falx, the contralateral hemisphere in the frontal region below the falx, and the base of the skull were lacerated. The final step involved the dissection of the corpus callosum and resection of the affected brain hemisphere.[1]

The application of cerebral hemispherectomy for seizure control was first introduced by McKenzie in 1938, who performed the procedure on a patient with infantile hemiplegia. Krynauw and colleagues provided the next instance of hemispherectomy as a seizure control alternative in 1950, when they demonstrated an 83.3% seizure control success rate in 12 affected adults with infantile hemiplegia.[2] This resulted in the widespread recognition of hemispherectomy as a surgical alternative for epilepsy control. Throughout the

following decade, hemispherectomy was utilized by a number of surgeons, and around 400 cases were documented.[3]

Despite its effectiveness in seizure control, the complications associated with hemispherectomy, including delayed hydrocephalus and superficial cerebral hemosiderosis, led to a wane in usage of hemispherectomy by the late 1960s.[3] These complications could have been brought about because removing parts of the brain could leave the subarachnoid and intraventricular spaces more susceptible to accumulating blood products.[4] This could create an environment similar to a subarachnoid hemorrhage, which could potentially induce hydrocephalus.[5] This complication could also present itself when bone removal is carried out toward the midline as reviewed by De Bonis and colleagues.[6] The observed complication remission ranged from as early as 1 year to as late as 20 years after surgery, and the rate of reported complications was approximately 18% to 35%.[4]

The notion of hemispherectomy as an unreliable surgical procedure was challenged by Rasmussen and colleagues in 1974 when they further modified the procedure: They excised the central cortex along with the temporal lobe and detached the residual ipsilateral neocortex from the basal ganglia and contralateral cerebral hemisphere.[7] This updated procedure is considered to be the inception of a new technique known as functional hemispherectomy: complete hemispheric disconnection was achieved without removing the entire hemisphere. The advantage of this technique was that, along with the seizure control benefits of anatomical hemispherectomy, fewer late-onset complications were observed. Rasmussen's technique directly preceded the modern hemispherotomy techniques used today.

Contemporary hemispherectomy procedures are modified versions of Rasmussen's functional hemispherectomy designed to minimize the amount of excised brain matter and postoperative complications. The current emphasis on smaller craniotomies with greater focus on disconnection rather than resection can be attributed to the small or maldeveloped ventricles often present in epilepsy patients (Table 12.1).[3] This has been augmented by advances in modern neuroimaging techniques, such as MRI, which have yielded more accurate and prompt diagnoses of epileptogenic substrates, including cortical dysplasia and Rasmussen encephalitis.[8]

ASSOCIATED COMPLICATIONS

Hemispherectomy is considered a sensitive surgical procedure due to associated postoperative complications, such as hydrocephalus. Due to the inherent risk, the procedure is only performed at select centers, which subsequently yields a small sample size. Lin and colleagues examined outcome trends associated with the procedure over a 10-year span (2000–2009) during which time 552 hemispherectomy procedures were performed (mean = 55.2 per year).[9] They examined the kids' inpatient database and found that 1.2 in 100,000 admissions underwent hemispherectomy in 2000. This figure had increased to 2.2 in 100,000 admissions by 2009 with no discernible trends in postoperative complications. The authors observed an in-hospital mortality rate of 0.9% overall, meningitis rate of 7.3% to 11.9%, and deep-vein thrombosis rate of 0% to 1%. Complication rates were consistently low throughout this period despite the fact that estimated annual hemispherectomy patient admissions had nearly doubled from 2000 to 2009. This strongly suggests the current techniques are stable and effective.

Hemispherectomy in pediatric cases has been long established with few instances of the procedure being carried out on adults. A comprehensive review of hemispherectomy procedures indicated that the mean age of hemispherectomy patients was 6.7 years old.[9] Pediatric hemispherectomy is more prevalent because of the Kennard effect, which suggests that a disruption in a developing brain can be functionally compensated elsewhere in the brain, exhibiting greater plasticity than an adult brain.[10] It is now understood that complex cognitive skills, such as visual processing and abstraction, can be implemented by a single hemisphere, which makes the adolescent brain an ideal candidate for cerebral resectioning.[11] Despite this, analysis of the unexcised brain is partially confounded by brain maturation dynamics, such that the relative impact of the two phenomena is difficult to quantify. Here, we report the results of a multimodal neuroimaging study aimed at comparing the brain volumetrics of unexcised brain structures in adolescents who underwent anatomic hemispherectomy to the corresponding volumetrics of age- and sex-matched healthy controls.

NEUROIMAGING

Neuroimaging plays a vital role in the initial diagnosis and follow-up of various neurodegenerative consequences that may require hemispherectomy. Modern neuroimaging techniques include structural and functional magnetic resonance imaging (MRI; Figure 12.1), computerized axial tomography (CAT or CT), photon emission tomography (PET), and single photon emission computed tomography (SPECT). These methods, often utilized in conjunction with each other, can provide detailed information about the health of a patient's brain unattainable through other measures. MRI is the most commonly used imaging technique today.

The first of these modern neuroimaging techniques was the CT scan, developed in the late 1960s by Godfrey Hounsfield and first used on a patient in 1971.[12] He adapted a reconstruction method called the algebraic reconstruction technique (ART), designed to approximate a solution to large systems of linear algebraic equations as the mathematical mechanism for his scanner. Using Americium 95 as a gamma source and a photon counter as the detector, the device registered 160 parallel readings across 180 angles, each 1° apart, yielding an 80 × 80 matrix of 3 × 3 × 13 millimeter voxels. The patient's head was covered with a rubber cap surrounded by water in order to reduce the range of detected X-rays. Modern iterations of CT

Table 12.1 Hemispherectomy and hemispherotomy techniques

Group 1: Complete cortical removal (anatomic hemispherectomy)	Subgroup A: Intraventricular approach (Dandy's technique)	• Ligation and sectioning of anterior circulation arteries and veins • Brain is disjoined from dura mater, frontal lobe is removed, corpus callosum is divided • Once the ventricular surface is identified, an incision is made through the corona radiata to reach the temporal and occipital lobes • Removal of the disconnected hemisphere
	Subgroup B: Extraventricular approach	• Initially employed to avoid basal ganglia injury but later used to prevent hemosiderosis • Sylvian fissure is exposed and an incision is made from the posterior part of Sylvian fissure to the vertex across the parietal lobe (Winston et al., 1970) • Plane of dissection is developed from the edge of insula below the cortex around the temporal horn to the falx above corpus callosum and temporal fossa dura mater • Various adaptations of the procedure are present, each of which involves resection around the temporal horns to keep them and related structures intact
Group 2: Disconnective techniques (functional hemispherectomy/ hemispherotomy)	Subgroup A: (Rasmussen's technique)	• Temporal lobe and central part of frontal and parietal lobes are removed • The remaining frontal and occipital lobe are disconnected subpially
	Subgroup B: Vertical approach	• Involves initiation of disconnection with a high parietal corticectomy • Further extends to the roof of lateral ventricle parasagittally via parenchyma • Complete corpus callosum fiber detachment and incision through corona radiata to reach the lateral ventricles • Removal of the middle structure of temporal lobe and frontal and occipital lobes are excised
	Subgroup C: Lateral approach (peri-insular hemispherotomy)	• Starts with subpial resection of supra-Sylvian and infra-Sylvian areas from the frontal and temporal lobes • Insula is exposed, an incision is made along the circular sulcus through white matter, exposing the surface of lateral and temporal ventricles • Lateral ventricle is exposed using cortical incisions along the temporal horn • Hemisphere is disconnected through the intraventricular space • Modifications of this method involve more effective exposure of the ventricular system

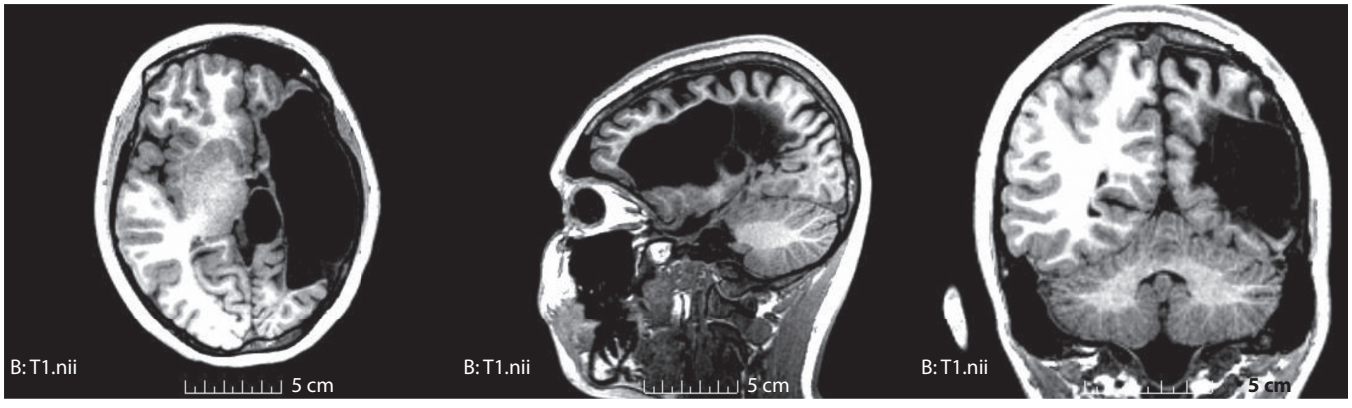

Figure 12.1 Axial, sagittal, and coronal MRI cross-sections of a brain after undergoing hemispherectomy.

scanners sport improved capabilities regarding speed, slice count, and image quality, which allow for more detailed data. Due to its wide availability in many medical centers around the world, potential hemispherectomy patients frequently undergo CT scans to elucidate neuroanatomical features.[13]

MRI, developed in the early 1970s through the work of Paul Lauterbur, Raymond Damadian, Peter Mansfield, and others, applies gradients across a magnetic field to invoke precession in the nuclear magnetic resonance (NMR) of hydrogen proton spins, allowing for the detection of radio waves emitted from these nuclei in the subject being observed.[14] MRI differentiates between aqueous solutions of varying density, which was a massive breakthrough in the field of neuroimaging. Contemporary MRI is stratified into two categories: structural (sMRI) and functional (fMRI). sMRI elucidates the anatomical structure of a subject's brain by measuring the hydrogen nuclei in the water of the brain. fMRI assesses the consumption of blood-oxygen-level dependence (BOLD), allowing for a quantifiable image volume representation of a brain's active regions. This allows for the observation of a subject's brain activity in real time. fMRI is commonly used as an investigative tool in hemispherectomy studies, specifically employed to determine the degree to which the procedure has impacted brain activity.[15] MRI measures both the spin–spin interactions, known as T_1 relaxation, and spin–lattice interactions or T_2 decay. T_1 relaxation is helpful to observe structural abnormalities whereas T_2 decay is utilized to better observe fluids and white matter (WM) patterns. The wide variety of MRI pulse sequences now available afford multiple options for emphasizing not only gray matter (GM), WM, and cerebrospinal fluid, but also identifies tissue contrast associated with TBI-related tissue alterations (e.g., edema, necrosis, hemorrhage, etc.), which lend themselves to rigorous quantification.[16,17]

Neuroimaging methods frequently play a key role in the diagnosis of brain dysfunctions that necessitate hemispherectomic intervention. In Rasmussen's encephalitis, for instance, MRI is used to determine unihemispheric focal cortical atrophy. Within months of onset of the harshest stage of Rasmussen's encephalitis, patients tend to exhibit unilateral enlargement of the ventricular system, best viewed using T_2-weighted MRI. Because hemispheric atrophy can be observed progressively, patients are typically scanned serially to better diagnose such diseases.[18] Additionally, EEG can be used to determine whether unihemispheric slowing and unilateral seizure onset is present in Rasmussen's encephalitis patients, demonstrating the importance of neuroimaging for looking at the longitudinal changes and postoperative complications.

Finding the precise location of the epileptic focal center is important to alleviate the symptoms of pharmacologically resistant posttraumatic epilepsy.[19] In particular, this remains a major challenge in cases in which a patient suffers from nonlesional epilepsy and extratemporal lobe epilepsy.[20] The main issue to be overcome with presurgical evaluation is separating the epileptic area from the otherwise functional cortex. The methodologies that are highly effective in carrying out these delineations, such as scalp EEG and intracranial EEG, are quite invasive and tend to elicit complications, including subdural hematomas, bleeding, and associated infections.[21] This is augmented by neuroimaging techniques, including MRI, PET, SPECT, and more recently, diffusion tensor imaging (DTI), which have significantly eased the process of locating specific brain networks that may service epileptic foci.[22]

HEMISPHERECTOMY PATIENTS

As an example of the issues involved in the processing of neuroimaging data from hemispherectomy patients, we present a series of six patients (five right hemispherectomy patients; five females; age range: 10 to 14 years; $\mu = 11.67$ years, $\sigma = 1.86$ years) who underwent this procedure to alleviate their pharmacologically resistant epilepsy. T_1-weighted MRI scans were acquired using a BRAVO-ASSET (IR-prepared FSPGR) sequence (1.5 T GE Signa HDxt scanner, TR = 9.31 ms, TE = 3.67 ms, TI = 450 ms, flip angle = 13°, slice thickness = 1 mm, matrix size = 256 × 256, 3-D acquisition, 100% sampling). Diffusion tensor imaging was also obtained in these subjects. Although depicted in the accompanying figures, these data were not formally subjected to quantitative analyses for this particular discussion. The healthy control group utilized consisted of 437 volunteers (238 males; age range: 10 to 15.92 years; $\mu = 12.96$ years, $\sigma = 1.80$ years) who underwent T1-weighted MRI scans as part of the PING project.[23] In what follows, we illustrate the data processing challenges associated with the hemispherectomy patients, their comparisons to healthy controls, attempts for overcoming them, and present intriguing original results.

DATA PROCESSING CHALLENGES

Traditional processing of neuroimaging data requires specific protocols and software programs; consequently, the prospect of processing hemispherectomy data presents novel challenges. Most software designed to process brain images operates under the assumption that the brain in question is intact, resulting in errors when attempting to process a partial brain. For this purpose, the Freesurfer (FS; http://surfer.nmr.mgh.harvard.edu) software package was used and applied via the LONI Pipeline workflow environment (http://pipeline.loni.usc.edu; Figure 12.2). FS, like other processing software, is dependent on the T1 MRI volume data being input to have come from generally healthy, intact brains. In cases in which this is not true, as in the case here, the derived statistics from FS are unlikely to be reliable. For FS to accept and process the image volumes, they need to be manipulated in a manner so that "whole brain" computations can be performed (shown in Figure 12.4), and more reliable results obtained for the intact brain tissue. We now describe this process.

First, all the images were reoriented such that any variations in the position of brain relative to the imaging field

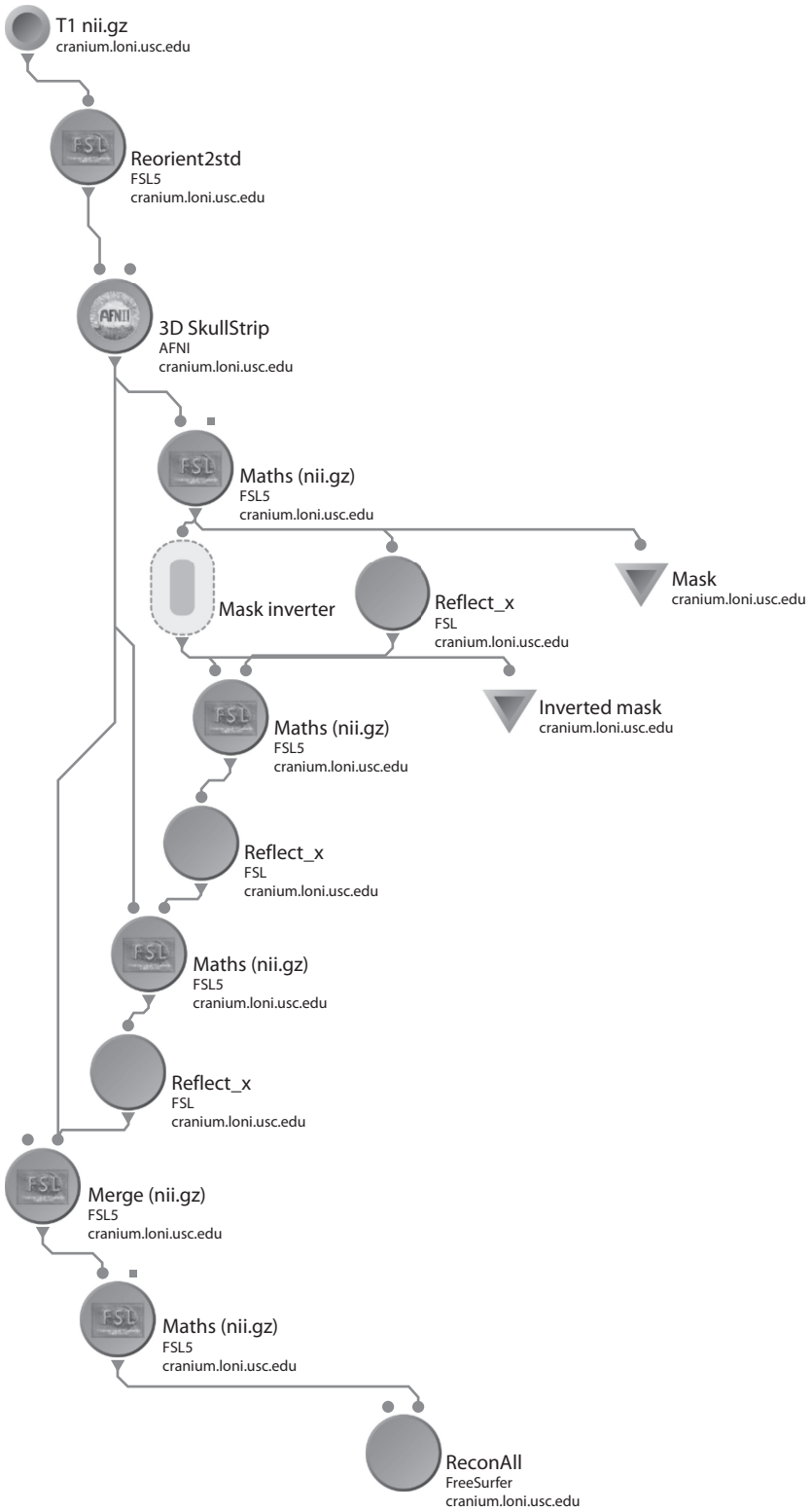

Figure 12.2 Hemispherectomy LONI Pipeline image volume data processing workflow.

of view were standardized. Then, in order to process the brain, it was subjected to skull stripping ("3D SkullStrip" in the Pipeline workflow in Figure 12.2) and a binary mask of the brain was generated. This binary mask would be used in later stages to extract information from the brain region that was originally present. After generating a mask, the brain and mask are inverted along the x-axis ("Reflect_x," "Mask Inverter") to "fill in" the region that had been excised. This is done by reversing the x-coordinate axis of the brain mask and taking the resulting mask's inverse. The inverse mask only selects the brain region that is missing and denotes all the other regions as 0. This results in only the excised hemisphere being "filled in." Reinverting the x-axis of this mask and applying it to the intact hemisphere extracts brain tissue from the intact hemisphere that has the same shape and the excised tissue absent due to surgical removal. Finally, this image volume is reinverted and then merged onto the original brain. This process results in a "full brain," which can be run reliably through FS, which will estimate a regional label map from the T_1 volume. Knowledge of the excised region via the mask of its volume can then be used to exclude all the information associated with this "fabricated" brain and subsequent statistics can be computed. Thus, for statistical analysis purposes, only the volumetrics associated with the cerebella and with the unexcised cerebral hemisphere were included. Specifically, the total volume of the GM, WM, and lateral ventricle in the unexcised hemisphere were examined. For the cerebella, the total GM and WM of each hemisphere were included in the analysis.

The null hypothesis assessed was that volumetric measurements of a study patient did not differ significantly from the average corresponding volumetrics of the control sample. To account for differences in head size across participants, all computed volumetrics were normalized by intracranial volume (ICV) within each subject. The left hemisphere (LH) volumetrics of each patient (when available) were statistically compared to the LH volumetrics

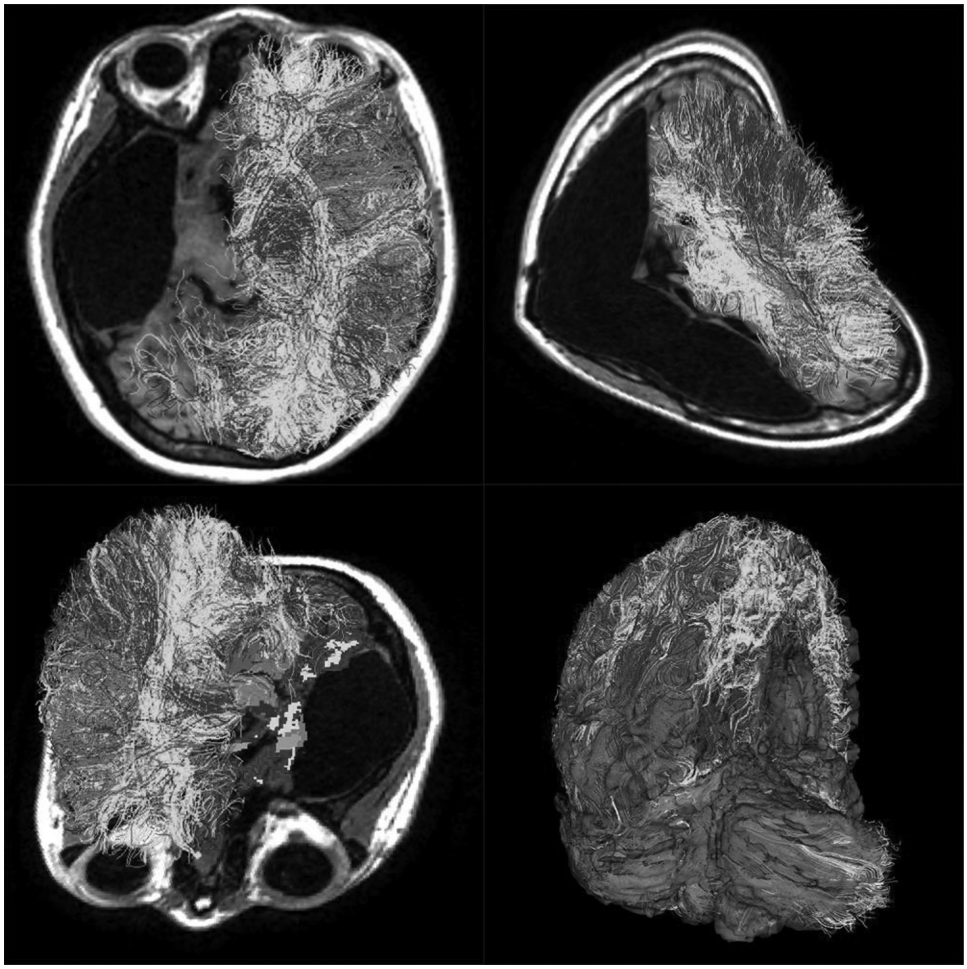

Figure 12.3 (Top left) Axial T1 cross section overlaid with tractography. (Top right) Orthogonal cross section of coronal and axial T1 with DTI tractography overlaid. (Bottom left) Axial T1 cross section overlaid with tractography and mask. (Bottom right) Model of hemispherectomy brain with tractography overlaid.

from the control group, and the same was done for right hemisphere (RH) volumetrics, thereby allowing us to partially control for the laterality-related confounding effects. Z scores were computed to situate the volumetrics of each study patient within the context of the healthy population and to test the null hypothesis of no volumetric difference between study patients and the healthy population.

RESULTS

Example outputs for one of the hemispherectomy subjects used here are shown in Figures 12.3 and 12.4. In five patients, the cortical GM and WM volume in the unexcised hemisphere were found to be statistically greater than in the healthy control group ($z > 2.65$, $p < 0.004$; Table 12.2). In all patients, the volume of the lateral ventricle in the unexcised hemisphere was found to be statistically larger than in healthy controls ($z > 1.63$, $p < 0.05$). The WM volume of the cerebellum contralateral to the excised hemisphere was not found to be significantly different from the healthy population. By contrast, in five patients, the GM volume of the cerebellum contralateral to the unexcised hemisphere was found to be significantly larger than in the healthy population ($z > 3.79$, $p < 7 \times 10^{-5}$). In five patients, the WM volume of the cerebellum ipsilateral to the excised hemisphere was found to be significantly smaller than in the healthy population ($z < -7.95$, $p < 10 \times 10^{-15}$). By contrast, in all patients, the GM volume of the cerebellum ipsilateral to the excised hemisphere was found to significantly larger than in control subjects ($z > 2.34$, $p < 0.001$).

DISCUSSION

Hemispherectomy has become an established surgical treatment for carefully selected pediatric patients who suffer from intractable and pharmacologically resistant epilepsy. Recent published perioperative data report low mortality and seizure reduction rates of 50%–89% with no major

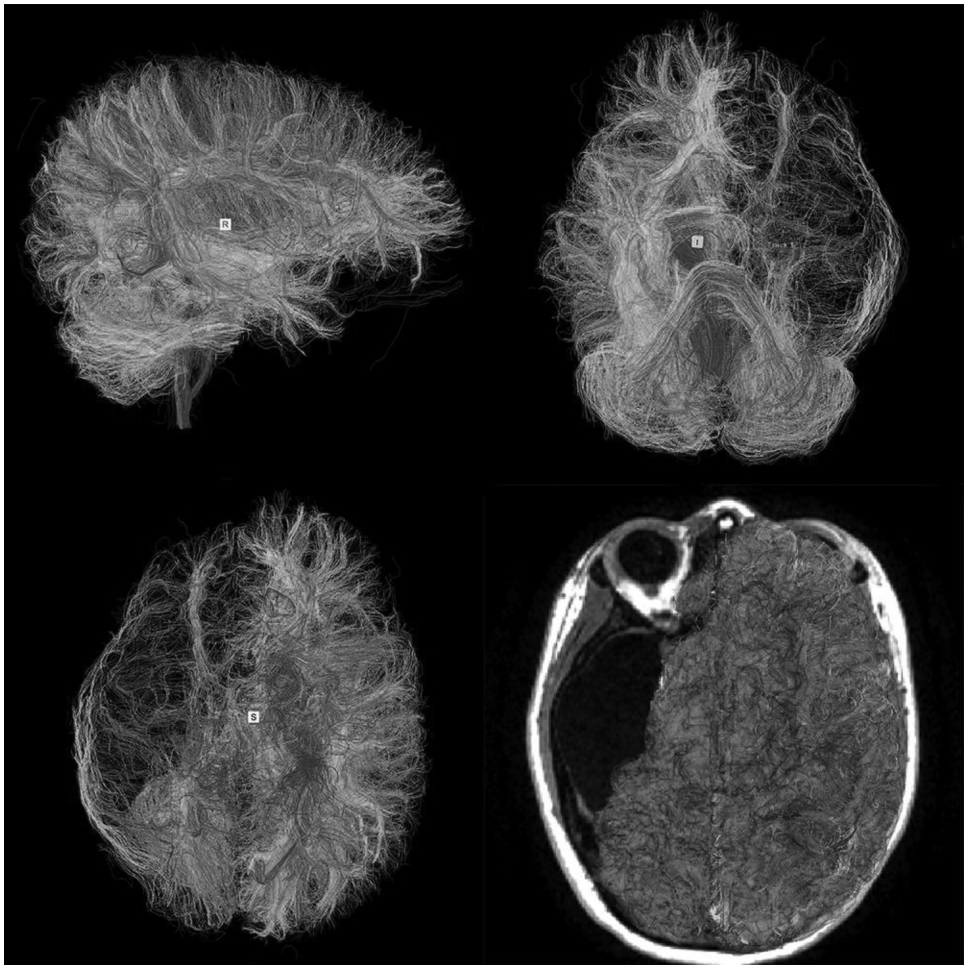

Figure 12.4 (Top left) Sagittal view of tractography of the unexcised hemisphere of a hemispherectomy patient. (Top right) Inferior view of tractography of hemispherectomy patient. (Bottom left) Superior view of tractography of hemispherectomy patient. The extraneous tracts visible in the excised hemisphere are from residual fibers not removed during hemispherectomy. (Bottom right) Complete overview of hemispherectomy with tractography and a model overlaid in the T_1 space. Extraneous tracts are absent here because the fibers are contained within the boundaries of the model.

Table 12.2 Z-scores for brain structures (compared to healthy controls)

Subject	Sex	Age	Affected hemi	Cort GM UEH	Cort WM UEH	UEH lat ventr	UEH cereb WM	UEH cereb GM	EH cereb WM	EH cereb GM
Patient 1	F	14	L	4.69**	7.38**	1.63	1.44	5.59**	3.64*	6.00**
Patient 2	M	14	R	−0.35	0.83	15.40**	−0.36	1.09	−8.95**	2.34
Patient 3	F	11	R	4.67**	3.83*	3.62*	0.61	4.76**	−8.77**	6.12**
Patient 4	F	11	R	8.22**	11.28**	4.86**	4.65**	17.99**	−7.95**	14.30**
Patient 5	F	10	R	3.43*	3.57*	3.65*	1.74	3.79*	−8.76**	5.85**
Patient 6	F	10	R	2.65*	4.04*	5.59**	0.89	7.13**	−8.81**	8.00**

Abbreviations: cereb: cerebellum, cort: cortical, hemi: hemisphere, lat: lateral, UEH: unexcised hemisphere, ventr: ventricle.
*significant at $p < 0.05$, **significant at $p < 0.001$.

trends reported with regard to postoperative complications.[9] Postsurgical improvement of cognitive and behavioral functions has been observed in children following hemispherectomy and suggests plastic reorganization of the brain.[24–28] For instance, changes in DTI metrics, such as fractional anisotropy and mean diffusivity, may reflect Wallerian and/or transneuronal degeneration of the WM tracts within the remaining hemisphere. In patients with acquired pathologies, postsurgical fractional anisotropy values have been noted to correlate positively with the time elapsed since the operation, indicating a greater ability for recovery in contrast to patients with congenital pathologies necessitating hemispherectomy.[29] Indeed, the use of neuroimaging has provided unique insights into the initial need for and the recovery outcomes of hemispherectomy.[27,30–36]

Due to unavailability of longitudinal data in our exploration here, it is uncertain whether the volumetric differences between our patients and the healthy population are brain changes specifically due to hemispherectomy although this possibility cannot be dismissed. The significant positive differences in cortical GM and WM volume in patients compared to controls are possibly due to the unexcised hemisphere tissue expanding into the space formerly occupied by the excised hemisphere. This is a plausible scenario in the absence of the mechanical forces that held the unexcised hemisphere in static equilibrium prior to the surgical intervention. Positive differences in lateral ventricular volume could be attributed to the expansion of the unexcised hemisphere into the vacant contralateral space, to cerebral atrophy in the unexcised hemisphere, or to a combination of these two phenomena. Positive differences in cerebellar GM and WM volume contralateral to the excised hemisphere may be due to compensatory reorganization of motor pathways following hemispherectomy.

In the case of the cerebellum ipsilateral to the excised hemisphere, the negative difference in WM volume may be associated with the loss of long-range connectivity between the cerebellum and the excised hemisphere. This is probable because the cerebellum lies above the decussation of the pyramids, such that severing WM connections (e.g., the corticospinal tract) above the decussation led to substantial loss of long-range connectivity between the cerebellum ipsilateral to the excised hemisphere and the rest of the nervous system. The positive significant difference in cerebellar GM volume between patients and controls may be indicative of mechanical expansion of the cerebellum into the supratentorial space previously occupied by the excised hemisphere, to cerebellar circuit rewiring, or to both.

The fact that the thalamus in the unexcised hemisphere was found to be statistically larger in patients than in the general population may be due to several factors. On one hand, it may indicate that the unexcised thalamus assumed a compensatory functional role subsequent to the hemispherectomy. On the other hand, because the thalamus is located very close to the medial wall (whose shape and location were presumably altered as a result of surgery), it is possible that the neural tissue of the thalamus in the unexcised hemisphere may have shifted location. This may have been the result of mechanical forces that pushed the thalamus farther into the space previously occupied by the excised hemisphere, thereby leading to a net increase in thalamic volume. Brain connections between the thalamus of the unexcised hemisphere and the thalamus of the excised one were clearly lost; it is thus possible that some of the space occupied by neuronal somata and by axons involved in such connections was occupied by cells that proliferated within vacated space in the thalamus due to phenomena, such as gliosis.

Two limitations of this examination are that 1) no presurgery MRI volumes of the patients are available to us and 2) a much larger sample of hemispherectomy patients is necessary to attempt statistical inferences about the dynamics of structural brain reorganization after this procedure. Nevertheless, our neuroimaging results provide interesting and useful insights into how the brains of these patients differ from those of healthy controls. The ability to assess differences between individual hemispherectomy patients and healthy controls may be useful as a preliminary step to the formulation of patient-specific treatment or rehabilitation protocols in this patient population.

CONCLUSION

Hemispherectomy is considered the most effective surgical procedure for treating pharmacologically resistant epilepsy.

For close to a century, hemispherectomy has evolved from anatomical to functional to present-day hemispherotomy in order to improve the effectiveness in alleviating seizures while simultaneously reducing postsurgical complications. Even though the procedure has been performed for many years, hemispherectomy continues to be a rare surgical procedure whose impact upon unexcised brain structures is poorly understood. In adolescents, this effect is partially confounded by brain maturational dynamics, such that the relative impact of the two phenomena is difficult to quantify. Despite this, hemispherectomy patients are often able to regain complete brain functionality, the success of which can be attributed to age at operation.

The observed alterations in brain structural volume postsurgery suggest several interesting implications. First, the fact that significant positive differences in cortical GM and WM volume in our subjects when compared to controls were observed indicates that the brain tends to reorganize itself in the event of considerable trauma. Nevertheless, much care is required in the processing of hemispherectomy neuroimaging data using automated processing tools. Future studies using a longitudinal neuroimaging design and larger sample sizes are likely to provide additional information of clinical utility.

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PART 2

Medical

13

Clinical management of the minimally conscious state

YELENA G. BODIEN, SABRINA R. TAYLOR, AND JOSEPH T. GIACINO

INTRODUCTION

Traumatic brain injury (TBI) is an acute event that triggers a chain of long-term consequences for affected patients and family members. Those who survive a severe brain injury may develop a prolonged disturbance in consciousness. Disorders of consciousness (DOCs) include coma, the vegetative state (VS), the minimally conscious state (MCS), and the posttraumatic confusional state (PTCS). This chapter focuses on the diagnostic, prognostic, and clinical management issues surrounding the care of patients in MCS. We begin by providing a brief overview of the clinical features of MCS, focusing on the differences that distinguish this condition from other DOCs. This is followed by a review of the various methods used to assess MCS and available treatments. The chapter concludes with a section on the clinical management of patients with MCS.

DISORDERS OF CONSCIOUSNESS: OVERVIEW AND DEFINITIONS

Recovery along the DOC continuum (i.e., coma, VS, MCS, and PTCS) can be difficult to predict. Some patients sequentially progress through each of these conditions as they recover, and others skip or plateau at specific points along the continuum. All four of these disorders reflect disturbances in arousal (i.e., wakefulness) and awareness (i.e., recognition of self and environment). Coma, first defined clinically by Plum and Posner in 1966,[1] involves a complete lack of arousal and awareness. The eyes remain closed, and behavioral responses are entirely reflexive; there is no discernible reaction to environmental or intrinsic stimulation. In addition, electroencephalography (EEG) data show no evidence of sleep–wake cycles. Reemergence of spontaneous eye opening signals the end of the comatose state and almost always occurs within 2–4 weeks. The clinical characteristics of VS were first described by Jennett and Plum in 1972,[2] with the most current diagnostic criteria established by the Multi-Society Task Force (MSTF) of the American Academy of Neurology in 1994.[3,4] Patients in VS experience periods of eye opening and sleep–wake cycles but do not demonstrate any behavioral signs of awareness of self or environment.[5] Prevalence rates for VS are highly disparate due to changes in prevailing diagnostic criteria, misdiagnosis, increasing duration of survival, and other factors.[6,7] Two recent systematic reviews that identified original studies, which collected data over variable time periods and in multiple countries, estimated the prevalence of VS to be between 0.2 and 3.4[8] and 0.2 and 6.1[9] cases per 100,000 inhabitants, respectively.

MCS is distinguished from VS by the presence of clear-cut behavioral signs of self or environmental awareness. The

conceptual underpinnings of MCS were operationalized by the Aspen Neurobehavioral Conference Workgroup in 2002.[10] The diagnosis of MCS requires reproducible behavioral evidence of command-following; discernible yes/no responses; intelligible verbalization; or nonreflexive movements, vocalizations, and affective behaviors that occur in contingent relation to specific environmental stimuli.[10] Recently, Bruno and colleagues[11,12] have argued that patients in MCS should be dichotomized into two subgroups: MCS plus (MCS^+), characterized by evidence of preserved language comprehension or expression, and MCS minus (MCS^-), in which patients fail to demonstrate any indication of language function but display at least one other behavioral sign of conscious awareness.[11] This subcategorization is supported by studies showing that MCS^+ patients have the higher rates of cerebral metabolism in language networks[12] and that preserved command-following is associated with functional connectivity of frontal networks.[13]

Prevalence rates for MCS are even more elusive than those for VS, due, in part, to the relatively recent description of this condition. Strauss and colleagues estimated the prevalence of MCS in the United States to be between 112,000 and 280,000, inclusive of adult and pediatric patients. It is important to note that this study relied on a proxy definition of MCS that was developed using a California State Developmental Disabilities Registry comprised of pediatric cases captured between 1988 and 1997. Prevalence was estimated by extrapolating from U.S. census data.[14,15] The paucity of published data on prevalence signals the need for a systematic approach to epidemiological studies of patients in VS and MCS.

The pathophysiology of DOC is not well understood; however, recent neuroimaging studies have implicated involvement of several different brain mechanisms linked to altered consciousness (see Di Perri et al.[16] for a review). Evidence of preserved cortical processing in both VS and MCS patients exists in the literature.[17–19] In general, level of consciousness appears to be heavily dependent on frontoparietal regions modulated by the thalamus[20–22] and the degree of connectivity of the default mode network (DMN).[23,24] A study by Di Perri and colleagues[25] also implicated the limbic system in altered consciousness. Findings indicated that limbic hyperconnectivity occurred concurrently with decreased DMN connectivity, an effect noted to be more prominent in patients in VS as compared to those in MCS. Existing diagnostic applications of neuroimaging remain limited by high false negative error rates,[26] unproven test–retest reliability, and restricted availability arising from the need for highly specialized equipment, personnel, and environmental controls.

The reemergence of a reliable yes/no communication system or the ability to use familiar objects in a functional manner marks the transition from MCS to PTCS.[10] In 1999, Stuss and colleagues[27] argued that PTCS should be distinguished as a condition unique from posttraumatic amnesia (PTA). The principal features of PTCS include temporal and spatial disorientation, distractibility, anterograde amnesia, impaired judgment, perceptual disturbance, restlessness, sleep disorder, and emotional lability.[28,29]

DIAGNOSIS OF MCS

Diagnostic assessment of patients with impaired consciousness significantly impacts prognosis, treatment, resource allocation, and end-of-life decisions. However, diagnostic error remains high,[30] and there are no objective markers that can definitively identify preserved or recovered conscious awareness. Consequently, clinicians rely on standardized and nonstandardized bedside examination to determine level of consciousness. Unlike patients in VS, those in MCS retain some evidence of self or environmental awareness. Because evidence of conscious awareness often drives health care decision making for families, clinicians, rehabilitation teams, and insurance companies, and prognosis is significantly more favorable for patients in MCS versus VS,[31,32] an accurate diagnosis is crucial to appropriate management.

Historically, diagnostic assessment has relied on qualitative analysis of bedside findings acquired by a single practitioner or professional team. Studies examining the rate of misdiagnosis consistently find that between 30% and 40% of patients diagnosed with VS are actually in MCS.[33–35] The dangers of failing to detect conscious awareness range from denial of authorization of rehabilitation services to premature end-of-life decisions.[36,37] Standardized behavioral assessment approaches have been developed to improve diagnostic accuracy although they vary in psychometric strength.[38] Advanced neuroimaging techniques designed to identify biological markers of conscious awareness provide complementary information, but these procedures remain under investigation and should not be used in clinical practice.

Clinical expertise

The definition and preliminary diagnostic criteria for MCS were published in 2002[10] and suggested that diagnosis and prognosis of patients with DOC should be established by an individual with experience in neurologic assessment of patients with impaired consciousness. Opinions from additional professionals familiar with this disorder were to be considered when making critical decisions surrounding clinical management issues. Nonetheless, recent studies have shown that, even when a clinical consensus is achieved by a team of professionals familiar with DOC, misdiagnosis remains high.[35] This likely reflects the difficulty of detecting voluntary behaviors (necessary for a diagnosis of MCS) in patients with fluctuating arousal, speech, and motor impairments; high frequency of spontaneous movements; poor initiation; and/or medical complications (e.g., tracheostomy, infection, medication changes, etc.). Consequently, the current recommendation for diagnosis of DOC discourages reliance solely on clinical expertise and emphasizes the use of standardized and validated behavioral rating scales.

Standardized behavioral assessment

Standardized behavioral assessment is recommended for monitoring recovery in patients with DOC[30,38] as there is increasing evidence that this approach minimizes diagnostic error. Serial assessment is often required to account for fluctuations in behavioral responsiveness that may result from changes in arousal level, time of day, medication regimen, medical status, and other factors. A variety of scales have been developed for assessing level of consciousness. Perhaps the most well known is the Glasgow Coma Scale (GCS),[39] comprised of three subscales that evaluate arousal as well as motor and verbal function. The GCS is used widely in the acute hospital setting but does not differentiate VS from MCS. The Rancho Los Amigos Scale Levels of Cognitive Function Scale,[40] used more frequently to predict outcome, assesses levels of awareness, cognition, behavior, and interaction with the environment from no response (level I) to purposeful appropriate response (level VIII). However, neither of these scales is standardized, and there is little evidence to support their reliability and validity.

A systematic review of behavioral assessment scales for DOC conducted by the American Congress of Rehabilitation Medicine (ACRM) compared the validity, reliability, and ability to predict functional outcomes of several measures.[38] The ACRM reviewers recommended the Coma Recovery Scale-Revised (CRS-R)[41] with minor reservation, and the Sensory Stimulation Assessment Measure (SSAM),[42] Wessex Head Injury Matrix (WHIM),[43] Western Neuro Sensory Stimulation Profile (WNSSP),[44] Sensory Modality Assessment Technique (SMART),[45] and Disorders of Consciousness Scale (DOCS)[46] with moderate reservation. Due to lack of content validity, standardization, and/or unproven reliability, the Coma/Near-Coma Scale (CNC),[47] Full Outline of UnResponsiveness Score (FOUR),[48] Comprehensive Levels of Consciousness Scale (CLOCS),[49] Innsbruck Coma Scale (INNS),[50] Glasgow-Liege Coma Scale (GLS),[51] Swedish Reaction Level Scale–1985 (RLS85),[52] and Loewenstein Communication Scale (LOEW)[53] were either recommended with major reservations or not recommended for assessment of DOC.

CRS-R

The CRS-R is a 23-item standardized rating scale comprised of six subscales that assess auditory, visual, verbal, motor, and communication functions as well as level of arousal.[41] The total score ranges from 0 to 23. The diagnostic criteria for MCS are embedded in the CRS-R and include reproducible or consistent movement to command, visual fixation, pursuit, object localization or recognition, localization to noxious stimulation, object manipulation, automatic motor response, intelligible verbalization, and nonfunctional/intentional communication. Emergence from MCS is indicated when accurate communication or functional use of objects is observed. Of the scales reviewed here, only the CRS-R provides guidelines for differential diagnosis of VS, MCS, and emergence from MCS as described by the Aspen Neurobehavioral Workgroup.[10] The CRS-R has well-defined administration and scoring procedures, good content validity, good item coherence, good inter-rater reliability, and excellent test–retest reliability. It is freely available at http://www.tbims.org/combi/crs/CRS%20Syllabus.pdf. A training DVD is available (coma@chu.ulg.ac.be) to promote competency in administration and scoring. Administration takes approximately 25 minutes (see Figure 13.1).

Each of the scales recommended with moderate reservation discussed below have either good or acceptable content validity and acceptable standardized administration and scoring procedures, but limited evidence is available regarding reliability or criterion validity.

SSAM

The SSAM assesses responsiveness over time to an array of sensory stimuli in severely brain-injured patients who do not consistently follow commands or communicate. Fifteen items divided into five subscales (visual, auditory, tactile, gustatory, and olfactory) are scored based on the level of eye opening and motor and vocalization responses to stimuli presented by the examiner.[42] The SSAM was designed to standardize sensory stimulation and assessment of responsiveness in treatment planning and research. Use of the scale does not require training, the measure is freely available and administration requires approximately 30 minutes.

WHIM

The WHIM is a behavioral scale that assesses and monitors recovery from coma through emergence from post-traumatic amnesia of severely brain-injured patients. It was designed to capture slow but subtle progress over weeks and months, bridge the gap between acute measures (i.e., GCS) and formal neuropsychological testing, aid in rehabilitation treatment planning, and inform long-term prognosis. Sixty-two items are categorized into 145 behaviors and six subscales (communication, attention, social behavior, concentration, visual awareness, and cognition).[43] The 62 items were derived by the authors following a longitudinal observational study of recovery of consciousness. Items are organized hierarchically such that the first item should appear before the second, which should appear before the third, etc. Data can be collected either by observation or formal testing, and standardized administration and scoring guidelines are provided but do not include diagnostic interpretation. The WHIM is available for purchase (http://www.pearsonclinical.co.uk/). Administration can take up to 1 hour, depending on severity of impairment.

WNSSP

The WNSSP assesses patients who demonstrate only generalized responses through those who are confused or agitated (i.e., Rancho Los Amigos Scale level II–IV). Thirty-two items are organized into six subscales (auditory comprehension, visual comprehension, visual tracking, object manipulation, arousal/attention, and tactile/olfactory).[44] Diagnostic interpretation guidelines of the subscale or total score are

JFK Coma Recovery Scale-Revised ©2004

Record form

This form should only be used in association with the "CRS-R administration and scoring guidelines" which provide instructions for standardized administration of the scale.

Patient:	Diagnosis:	Etiology:
Date of onset:	Date of admission:	

	Date															
	Week	ADM	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Auditory function scale																	
4–Consistent movement to command*																	
3–Reproducible movement to command*																	
2–Localization to sound																	
1–Auditory startle																	
0–None																	
Visual function scale																	
5–Object recognition*																	
4–Object localization: reaching*																	
3–Visual pursuit*																	
2–Fixation*																	
1–Visual startle																	
0–None																	
Motor function scale																	
6–Functional object use†																	
5–Automatic motor response*																	
4–Object manipulation*																	
3–Localization to noxious stimulation*																	
2–Flexion withdrawal																	
1–Abnormal posturing																	
0–None/flaccid																	
Oromotor/verbal function scale																	
3–Intelligible verbalization*																	
3–Vocalization/oral movement																	
1–Oral reflexive movement																	
0–None																	
Communication scale																	
2–Functional: accurate†																	
1–Non-functional: intentional*																	
0–None																	
Arousal scale																	
3–Attention																	
2–Eye opening without stimulation																	
1–Eye opening with stimulation																	
0–Unarousable																	
Total score																	

*Denotes MCS

†Denotes emergence from MCS

Figure 13.1 Coma Recovery Scale–Revised face sheet demonstrating the six subscales, 23 scale items, and behaviors that suggest a diagnosis of minimally conscious state or emerged from minimally conscious state.

not provided. The measure is freely available (http://www.coma.ulg.ac.be/images/wnssp.pdf) and requires approximately 45 minutes to administer.

SMART

The SMART is a clinical tool specifically designed to identify potential awareness in adults who are in VS and to identify functional and communication capabilities of patients in MCS. The SMART is comprised of two components: 1) informal gathering of information from family and caregivers, including observed behaviors and information pertaining to the patient's premorbid interests and likes and dislikes, and 2) 10 sessions within a 3-week period of observation of behavioral responses during which assessment of sensory (visual, auditory, tactile, olfactory, and gustatory), motor, communication, and arousal functions is conducted.[45] Twenty-nine standardized techniques are used for assessing these domains and yield a suggestive diagnosis as well as treatment guidelines. The SMART must be purchased, and administration requires submission of a work-based portfolio and a 5-day training course in the United Kingdom (http://www.rhn.org.uk/our-work/our-services/assessments/smart/smart-training/).

DOCS

The DOCS is a bedside tool that assesses the continuum of neurobehavioral functioning in unconscious persons over time, detects subtle changes in behavior, distinguishes between volitional and random behaviors, and identifies factors that predict and influence recovery. This scale consists of 23 test stimuli intended to assess social knowledge, taste and swallowing, olfactory, proprioceptive/vestibular, tactile, auditory, and visual functions. Responses to each stimulus are scored as "no response," "generalized response," and "localized response."[46,54] Long, short, and research versions of the scale are available along with free access to the administration manual: http://www.queri.research.va.gov/ptbri/docs_training/. Approximately 45 minutes are required for administration.

Individualized quantitative behavioral assessment

Individualized quantitative behavioral assessment (IQBA) applies the principles of single-subject research design to detect volitional behavior in patients who do not clearly demonstrate such behaviors on standardized assessment.[55] Clinical questions are posed by the treating team or family in response to informal observation suggesting the possibility of volitional behavior. An individually tailored assessment protocol with operationally defined behaviors is subsequently developed and administered. For example, a patient may appear to be following instructions to move the fingers of the right hand but not with sufficient frequency, consistency, or temporal contiguity required to clearly differentiate this behavior from random movement. Following operational definition of the stimuli, behavior, and response criteria, a systematic assessment protocol is administered to distinguish volitional from spontaneous and unrelated stimulus-induced occurrences of the behavior. Statistical analysis is conducted to determine whether there is a significant difference between the conditions (i.e., command, unrelated command, no command) under which the behavior occurs.

Advanced neuroimaging and neurophysiology (PET, fMRI, EEG)

The inherent limitations of bedside assessment of patients diagnosed with DOC coupled with the advancement in neuroimaging and neurophysiological techniques aimed at assessing brain function have led to several investigations of the diagnostic utility of positron emission tomography (PET), functional magnetic resonance imaging (fMRI), and electroencephalography (EEG) in this population.

PET imaging, which allows for visualization of brain metabolism and is therefore a proxy for synaptic firing, has shown bilateral metabolic dysfunction in frontoparietal networks in patients diagnosed with VS. On the other hand, patients in MCS maintain at least partially preserved metabolic function of this circuitry.[56–59] fMRI capitalizes on the coupling between deoxyhemoglobin concentrations and neuronal firing to produce maps of blood oxygen levels that can be interpreted as maps of brain activity. Reproducible patterns of brain activity are observed in response to task demands. fMRI studies have used language[60] and mental imagery tasks[61] to investigate covert command-following and suggest that task-evoked brain activation patterns may have diagnostic utility in DOC (see Figure 13.2). Furthermore, some patients diagnosed as VS on bedside assessment may actually retain conscious awareness based on fMRI findings.[61] One study comparing the diagnostic accuracy of these two imaging methods found PET to be more congruent with bedside assessment and more sensitive to detecting MCS than fMRI.[62]

EEG records brain activity via electrodes placed on the scalp and has relied on mental imagery to evoke patterns of electrical activity that may distinguish patients in VS and MCS.[63,64] Recent advances in EEG-based brain–computer interface paradigms support the use of this technique for establishing reliable command-following and communication in patients who do not exhibit these behaviors on bedside assessment.[65]

Although evidence from PET, fMRI, and EEG research studies[61,62,66] has been promising, the clinical utility of these measures for diagnostic and prognostic purposes remains unclear. Advanced neuroimaging techniques have not been validated sufficiently in a clinical context, and further investigation is necessary prior to diagnostic or prognostic application.

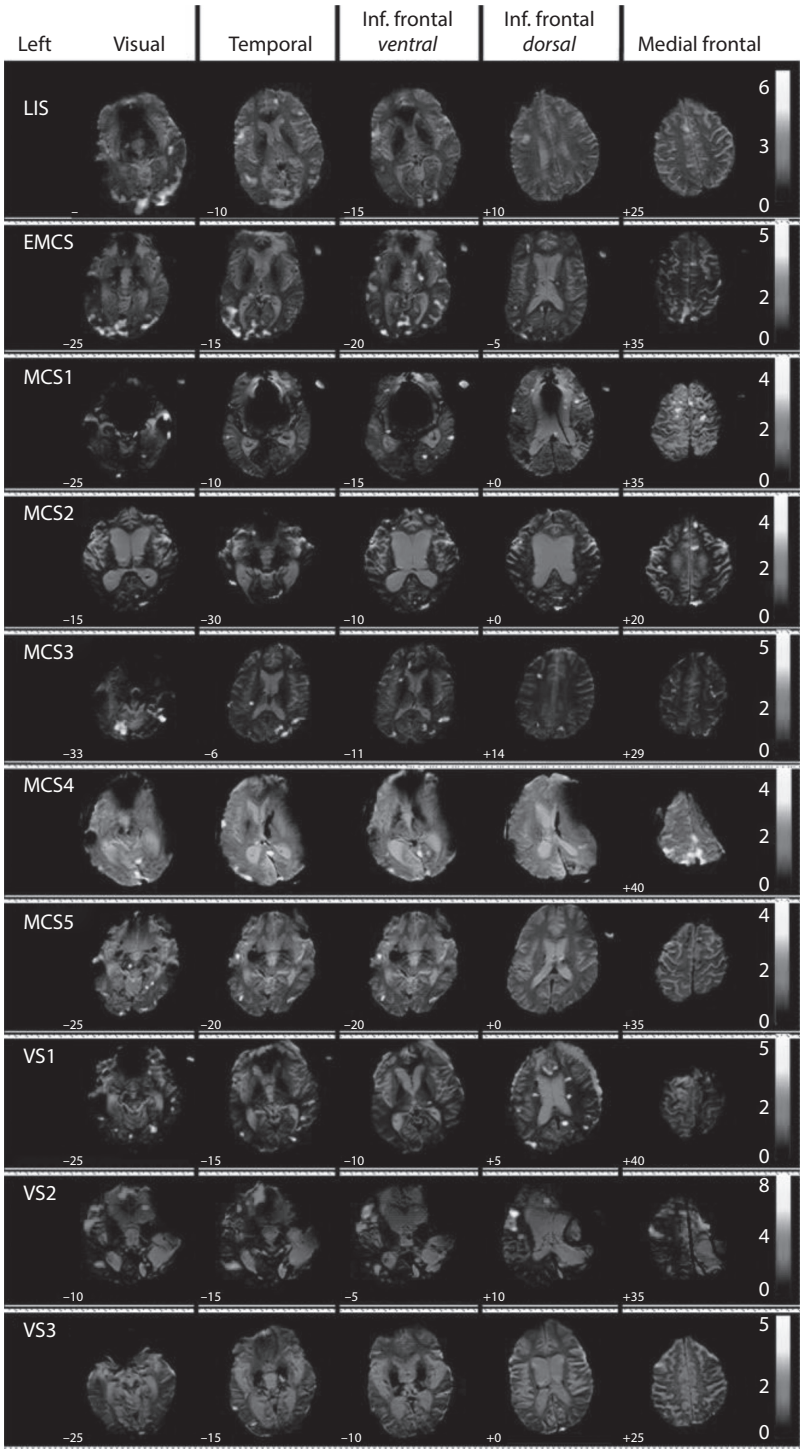

Figure 13.2 (See color insert.) Colored voxels indicate blood oxygenation level-dependent (BOLD) responses elicited by the covert picture naming task. Activations are overlaid on each patient's brain and shown in a representative slice for each anatomic area (top row). Color bars reflect the range of BOLD signal intensity changes with corresponding *t* values. EMCS = emerged from minimally conscious state; LIS = locked-in syndrome; MCS = minimally conscious state; VS = vegetative state. (From Rodriguez Moreno, D., Schiff, N. D., Giacino, J., Kalmar, K., and Hirsch, J., A network approach to assessing cognition in disorders of consciousness, *Neurology*, 2010 Nov 23; 75(21), 1871–1878. Wolters Kluwer Health Lippincott Williams & Wilkins. Reprinted with permission. Copyright 2010 by AAN Enterprises, Inc. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2995384/.)

CLINICAL INTERVENTIONS

There are currently no standardized, evidence-based recommendations or guidelines for treatment of patients with DOC. Most studies have significant methodologic flaws, including omission of adequate controls (i.e., placebo conditions) to guard against various sources of bias. Nevertheless, some studies suggest that certain rehabilitative interventions are advantageous and may promote recovery of consciousness, especially in patients diagnosed with MCS. There is also some evidence that intensive, task-oriented rehabilitation may lead to improved functional recovery.[67,68] The Royal College of Physicians has also published clinical guidelines based on expert opinion for management of prolonged DOC (https://www.rcplondon.ac.uk/resources/prolonged-disorders-consciousness-national-clinical-guidelines). It should be noted, however, that these recommendations are based on a relatively small literature base and will require further investigation prior to establishment of formal evidence-based guidelines.

Prior to initiating treatment, the clinician should be certain that a thorough, standardized, and systematic assessment has been conducted to establish an accurate diagnosis. In addition, treatable causes of poor responsiveness and arousal (i.e., hydrocephalus, seizure activity, metabolic dysfunction, excessive sedating medications) should be ruled out. Pain may also be a contributing factor to poor behavioral output and should be closely monitored using a validated assessment tool (i.e., Nociceptive Coma Scale–Revised[69]) specially designed for patients with DOC.

Treatment strategies can be divided into those that aim to 1) minimize medical complications that may mask cognitive level and/or hinder recovery of consciousness, 2) regulate sensory input by controlling the environment, and 3) alter brain activity via neuromodulation.

Avoiding complications

During inpatient rehabilitation, more than 80% of DOC patients experience at least one medical complication.[70] Consequently, it is essential that rehabilitation efforts focus on the identification and management of complications associated either directly with the brain injury (i.e., paroxysmal sympathetic hyperactivity, tone, and contractures) or with prolonged immobility and hospitalization (i.e., infection). Paroxysmal sympathetic hyperactivity (or dysautonomia), infection, and hypertonus are among the most common complications. Dysautonomia is a disturbance of the sympathetic nervous system that includes markedly increased heart rate, respiratory rate, blood pressure, and diaphoresis. Pharmaceutical agents such as morphine and beta-blockers may prevent these symptoms; however, these medications may also have sedative properties that decrease behavioral output and can mask level of conscious awareness. Nonpharmaceutical treatment may include environmental management and avoidance of triggers that lead to episodes of storming. Aspiration pneumonia, which is associated with tracheostomy, swallowing disorders, and diminished cough reflex, requires readmission to an acute care setting and may be life threatening. Elevating the head of the bed, modifying feeding schedules, and frequent oral care can help prevent episodes of aspiration pneumonia[71] (see also http://www.aacn.org/wd/practice/docs/practicealerts/prevention-aspiration-practice-alert.pdf?menu=aboutus). Spasticity and contractures, apart from being painful, may limit the capacity to respond to motor commands, leaving a false impression of failure to comprehend language or inability to initiate behavioral activity. There is some evidence that these symptoms may be managed with passive range-of-motion and serial casting, pharmacological agents (i.e., botulin toxin, baclofen), and other medical interventions, such as tendon lengthening.[72]

Sensory stimulation/regulation

The results of prior research investigating the use of sensory stimulation techniques (controlled presentation of multimodal stimuli) to enhance responsiveness neither supports nor refutes the effectiveness of this approach to treatment.[73] The existing evidence base is compromised by important methodologic weaknesses that prevent determination of effectiveness. Although there are no published reports of adverse events arising from sensory stimulation, overstimulation may trigger autonomic storming and a subsequent decline in responsiveness. Attention to sensory regulation (versus stimulation) is important as sensory stimulation can cause or exacerbate restlessness and agitation. Environmental management strategies should be employed to reduce excessive sensory input and foster appropriate behavioral output.

Neuromodulation

A variety of techniques for modulating brain activity in patients with DOC have been explored; these range from pharmaceutical to electrical and magnetic stimulation. There is a small but growing evidence base supporting the use of pharmacologic agents to promote recovery of consciousness. Three main classes of drugs have been investigated: dopaminergic, gabaergic, and serotonin/noradrenalin reuptake inhibitors.[74] One randomized controlled, multicenter open-label trial showed that amantadine hydrochloride was associated with earlier recovery of consciousness in posttraumatic patients diagnosed with DOCs compared with a placebo group during the active treatment phase[75] (see Figure 13.3). There have also been some reports that administration of zolpidem may induce arousal in patients with impaired conscious awareness; however, only a very small number of patients show a response to the medication.[76] In higher-functioning patients, methylphenidate may improve attention and speed of processing.[77] However, with the exception of the amantadine hydrochloride trial,[75] most studies investigating treatment effectiveness in DOC are single-case or open-label and do not include well-controlled placebo conditions or randomization.

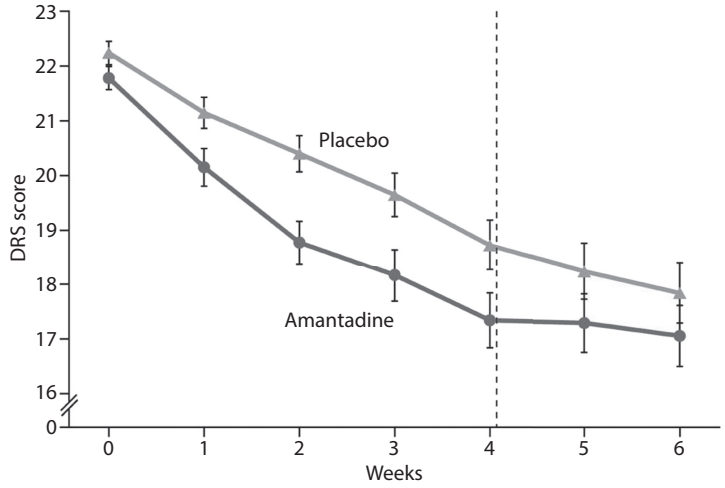

Figure 13.3 Amantadine hydrochloride significantly improves rate of recovery in moderate-to-severe TBI subjects as measured by the disability rating scale (DRS),[78] a reliable and valid measure for impairment, disability, and handicap in which subjects with higher scores are more disabled. (From Giacino, J. T., Whyte, J., Bagiella, E. et al., Placebo–controlled trial of amantadine for severe traumatic brain injury, *New England Journal of Medicine*, 366(9), 819–826, Copyright 2012 Massachusetts Medical Society. Reprinted with permission. http://www.nejm.org/doi/full/10.1056/NEJMoa1102609.)

When medication trials are conducted, control conditions should be instituted to help distinguish treatment responses from random or nonspecific fluctuations in behavior. Control conditions include establishing a stable baseline before exposing the patient to treatment, avoiding concurrent use of other centrally active agents that could suppress or potentiate a response, using a validated assessment measure to monitor changes in performance, and blinding staff responsible for collecting outcome data to the nature and timing of treatment. Clinicians should always consider the relationship between the potential benefits and adverse effects of a given treatment intervention.

In addition to pharmaceutical interventions, electrical and magnetic stimulation techniques have been investigated to improve recovery of function after severe brain injury. One pilot study found that deep brain stimulation applied to the central thalamus via neurosurgically implanted electrodes increased behavioral output in a patients in MCS.[79] Application of repetitive transcranial magnetic stimulation, a noninvasive method that stimulates cortical tissue using magnetic fields, has also shown promise for improving conscious awareness,[80–82] and clinical improvement in patients with DOC has been shown following treatment with transcranial direct current stimulation.[83] Despite these advances and encouraging results, these methods have not been clinically approved for use in DOC and should only be applied in the context of approved research studies with full ethical and procedural oversight of an institutional review board.

Despite the many clinical trials and case reports investigating treatment options in DOC, evidence for the use of these treatments (with the exception of amantadine hydrochloride) in this patient population is weak. Future studies will need to focus on improving experimental designs to include randomization, placebo-controlled groups, and large samples across multiple sites.

CONCLUSION

Management of patients with DOC is complicated and requires multidisciplinary expertise from a team of professionals with specialized training in brain injury. Physicians should be aware of the most common medical complications that arise from severe brain injury and should be attentive to factors that may confound assessment results and result in underestimation of cognitive status. The rehabilitation team also requires specialized training, especially in administration of standardized metrics designed to detect behaviors associated with conscious awareness and communication ability. Clinicians should be cognizant of the possible adverse effects of treatment strategies as there are currently no evidence-based guidelines to assist with decision-making. More robust involvement of clinicians in research is also needed to advance the pace of discovery and improve the prospects for functional recovery in this population.

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14

Neuropharmacologic considerations in the treatment of vegetative state and minimally conscious state following brain injury

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INTRODUCTION

The treatment of individuals with prolonged disorders of consciousness following trauma or other insults to the brain remains a challenge. This chapter reviews definitions of low arousal states, the neurophysiology of consciousness, the pathophysiology of alterations of consciousness, and the basic underlying neurotransmitter functions that may be impacted by injury. Neurotransmitter systems provide a potential target for pharmacologic manipulation. The goal of drug treatment is to improve wakeful awareness, thereby facilitating neurologic recovery. Medications that may be useful in the treatment of disorders of consciousness are reviewed and organized by the neurotransmitter systems through which they exert their effects. Although still in its infancy, our understanding of neurotransmitter interactions and cognitive function will serve as the foundation upon which novel drug therapies will be developed.

DEFINITIONS OF COMA, VEGETATIVE STATE, MINIMALLY CONSCIOUS STATE, AND FUNCTIONAL LOCKED-IN SYNDROME

Recovery from traumatic and nontraumatic brain injury is characterized by gradual emergence from coma. Depending upon the severity of the underlying brain damage, patients may transition from coma to vegetative state to minimally conscious state (MCS) to severe disability, and ultimately to good recovery. However, individuals may also plateau at any point along this continuum.

Coma is a state in which the patient is neither awake nor aware.[1] Comatose patients demonstrate no meaningful interaction with the environment. No purposeful movement is observed. No command-following is seen. The eyes remain closed even in the presence of noxious stimulation, and no sleep-wake cycles are observed. After brain injury, coma is typically a self-limited condition that evolves to vegetative state or higher levels of consciousness.

The term *vegetative state* was first introduced by Jennett and Plum[2] in 1972. It is defined as a condition of unconsciousness devoid of cognitive content and characterized by wakefulness without awareness. Vegetative state is also known as unresponsive wakefulness syndrome. The individual in a vegetative state demonstrates eye opening and gradually develops sleep–wake cycles. Spontaneous, nonpurposeful motor activity may be seen. Vegetative patients cannot comprehend language, nor can they communicate. Evidence of reproducible, purposeful responses to visual, auditory, tactile, or noxious stimuli are absent.[3] Roving eye movements and brief, unsustained visual tracking may be observed. One of the first signs of emergence from vegetative state is the appearance of sustained visual pursuit.[4]

MCS is a condition in which unequivocally meaningful responses are observed although on an inconsistent basis. MCS is a clinical diagnosis that requires behavioral evidence of meaningful interaction. This may include sustained visual pursuit; command-following; motor responses, such as reaching toward an object; intelligible verbalization; or the use of gestures to communicate.[5] MCS is sometimes misdiagnosed as vegetative state because bedside verification of meaningful responses can be difficult in patients who exhibit daily fluctuations in consciousness and who have meager available motor repertoires with which to follow commands.[5–7] Serial examinations over time and the use of a reliable standardized neurobehavioral rating scale are therefore recommended to improve diagnostic accuracy. Nevertheless, functional magnetic resonance imaging (fMRI) has demonstrated willful patterns of cortical activation consistent with a degree of preserved awareness in a small number of traumatically brain-injured patients who appeared vegetative by clinical criteria. Thus, fMRI may be a useful adjunct in distinguishing vegetative state from MCS.[8] Although clinical assessment with appropriate behavioral scales remains the gold standard for diagnosing disorders of consciousness, up to 35%–40% of patients are still misdiagnosed as being in vegetative state.[7] Neuroimaging (fMRI and positron emission tomography) and electrophysiologic techniques (EEG and evoked potentials) are likely to play a more prominent adjunctive role in the definitive diagnosis of disorders of consciousness in the future. Individuals with no detectable behavioral signs of meaningful interaction who demonstrate preserved cognitive processes using these technologies can be described as functionally locked in. This is not to be confused with locked-in syndrome with pontine involvement and intact cortical function.

Emergence from MCS occurs when a patient is capable of reliably and consistently demonstrating the use of at least two common objects or accurate yes/no responses (verbal or gestural) to simple questions on two consecutive evaluations.[5]

NEUROPHYSIOLOGY OF AROUSAL AND CONSCIOUSNESS

Consciousness is a state of awareness dependent upon adequate arousal mechanisms, functioning selective attention, and the ability to perceive and interpret sensory information from the world around us. Arousal, the foundation of consciousness, depends upon multiple connections between the ascending reticular activating system (ARAS) and the cortex via subcortical relay stations. The ARAS originates in the brain stem and exerts its effects on higher cortical centers by way of collateral projections through the thalamus, posterior hypothalamus, and basal forebrain. The brain stem ARAS is comprised of several distinct nuclei that rely on a number of different neurotransmitters to activate rostral brain regions. Thus, redundancy is built into the systems that support our most basic cognitive functions.

Dorsal projections from the brain stem ARAS reach the thalamus. The thalamus serves as the main relay and filtering station for ascending sensory information. Without the thalamus, most sensory input would not reach the cortex. Activation of the thalamic nuclei by cholinergic and glutaminergic fibers of the ARAS facilitates transmission of sensory input to higher cortical regions. The thalamic nuclei have both afferent and efferent connections with the cerebral cortex and brain stem. The thalamic reticular nucleus, in particular, is involved in the process of sensory gating. Gating of the stream of sensory data allows attention to be selectively focused on some aspects of sensory input and not others. The ascending pathways from the thalamus to the primary sensory areas of the cerebral cortex are predominantly glutaminergic. From the primary sensory areas, collateral connections proceed to the sensory association areas, where information is processed, interpreted, and consciously experienced.

The projections from the ventral ARAS modulate basal forebrain activation via catecholaminergic, glutaminergic, and cholinergic neurotransmission. Projections from the hypothalamus to the basal forebrain facilitate arousal through the release of histamine and orexin. The basal forebrain is located on the medial and ventral surface of the cerebral hemispheres. It acts as a ventral extrathalamic relay station between the ARAS and the cerebral cortex. The afferent connections from the basal forebrain to the cerebral cortex can be conceptualized as the most rostral part of the ARAS. These neural networks mediate arousal and awareness through both cholinergic and gamma aminobutyric acid (GABA)-ergic neurotransmission. Finally, additional connections with the limbic system as well as regions

involved in memory and executive function allow us to interact with our environment in a genuinely meaningful way.

Given the widespread regions involved in the maintenance of wakefulness and awareness, persistent disorders of consciousness may be the result of diverse pathology within the central nervous system. Injury may be seen in any part of the neuronal network important for arousal.

Adams et al.[9] undertook a detailed neuropathologic study of the brains of 49 patients who remained in vegetative state until their deaths 1 month to 8 years after an acute brain insult. Although diffuse axonal injury was sometimes seen, the more common findings in this study were damage to the major relay nuclei of the thalamus or the subcortical white matter tracks. A few cases were identified in which the cerebral cortex and the brain stem were both of normal appearance. The authors concluded that damage to the thalamus essentially severed the connections between any preserved functioning cortex and other cortical or subcortical regions, resulting in vegetative state. Interestingly, neuropathologic studies of individuals in MCS have shown less consistent thalamic involvement, indicative of relative sparing of corticothalamic connections.[10]

Damage to the tegmentum of the brain stem, an area comprising part of the ARAS, may also result in loss of consciousness. The combination of injury to the brain stem, basal ganglia, and thalamus increases the likelihood of a persistent low response state.[11,12]

The mesocircuit hypothesis has been offered to explain alterations of consciousness and how some medications work to improve an individual's level of consciousness.[13,14] After severe brain injury, the anterior forebrain is downregulated due to neuronal death and the disruption of neuronal networks involving the thalamus. When thalamocortical, corticostriatal, and thalamostriatal outflow is reduced, afferent drive to the medium spiny neurons of the striatum is withdrawn. This, in turn, decreases the inhibitory input from the striatum to the globus pallidus interna. Consequently, unchecked firing of the globus pallidus interna inhibits the relay neurons of the thalamus, contributing to persistent alterations of consciousness.[15]

FUNCTIONAL NEUROIMAGING IN DISORDERS OF CONSCIOUSNESS

Positron emission tomography (PET) and fMRI have identified different activation patterns in the brains of patients in vegetative state and MCS.[16–20] Patients in MCS demonstrate cortical activation similar to healthy controls, suggesting a preserved capacity for active cognitive interaction.

Neuroscience has moved beyond simply identifying what brain regions correlate with specific functions and activities and is now focused on the study of brain networks and connectivity, both structural and functional. Neuronal networks involving the cerebral cortex, thalamus, and striatum are essential to achieving conscious awareness. Severe brain injury may be associated with neuronal damage to the regions that regulate consciousness and/or a reduction in the connectivity of consciousness-related networks, leaving patients unable to emerge from vegetative or minimally conscious state. Raichle et al.[21] used fMRI to demonstrate that a particular network, called the default mode network (DMN), is deactivated when subjects are engaged in cognitive tasks and activated during periods of rest with the eyes closed. The DMN is comprised of the posterior cingulate cortex, precuneus, temporoparietal regions, medial prefrontal cortex, and parahippocampal gyri. Deactivation of the DMN during goal-directed activities is produced by action of the GABAergic system. After brain injury, the degree of preserved DMN connectivity seen on fMRI, PET, and SPECT appears to be related to level of consciousness.[22,23] DMN deactivation appears to be absent in patients in vegetative state and partially preserved in those in MCS.[24–27] However, its usefulness in accurately differentiating vegetative state from MCS in individual patients is limited.[28]

Coleman et al.[29] used fMRI to determine if patients in vegetative state retain some aspects of language comprehension. Indeed, some evidence of activation of the primary auditory cortex was noted in response to spoken language. However, the authors conceded that these findings did not imply actual language comprehension or consciousness. For conscious awareness of speech to occur, language must be "heard" in the auditory primary cortex, recognized in the auditory association cortex, and finally comprehended in Wernicke's area. Laureys et al.[30] found that, although auditory primary cortices are activated by auditory stimulation in the patient in vegetative state, the higher order association areas were not. They concluded that these functional disconnections preclude the integrated processing necessary for understanding, reflection, and awareness. Consistent with this view is the finding of improvement in disrupted connections between thalamic nuclei and their projections to the prefrontal and cingulate cortical regions in patients who have recovered consciousness.

Monti et al.[8] studied 54 patients with severe brain injuries, including 23 in vegetative state and 31 in MCS. fMRI was used to assess each patient's ability to reliably and repeatedly perform motor imagery (for example, imagining swinging an arm to return a tennis ball back and forth with an instructor) and spatial imagery (for example, imagining walking from room to room in their home and visualizing all they would see there). Among the 54 patients, five were identified who could willfully modulate their brain activity. Of these five patients, four had carried a diagnosis of vegetative state prior to the study, and all five had sustained traumatic brain injuries. The four vegetative patients who were able to demonstrate cognitive awareness were clinically reassessed, and two of them exhibited some behavioral indications of consciousness. The remaining two patients remained unresponsive on repeated clinical bedside evaluations. Thus, functional neuroimaging can detect unambiguous signs of consciousness in individuals who clinically appear to be in vegetative state. Additional tests were conducted on one of the patients who was initially thought to

be in vegetative state but who was found to be in MCS on subsequent examination. That patient was able to modulate his brain activity on fMRI to answer yes/no questions. A recent validation study comparing PET imaging and fMRI concluded that fMRI is less sensitive at diagnosing MCS (45%) than PET (93%).[31]

PROGNOSIS OF DISORDERS OF CONSCIOUSNESS

In 1994, the Multi-Society Task Force on Persistent Vegetative State (PVS)[32] performed a retrospective analysis of available outcome data for individuals who remained in vegetative state for 1 month or more following either traumatic or nontraumatic injuries to the brain. They found that the prognosis for recovery was directly related to the duration of vegetative state and its cause.

Outcome data was available for 434 adult patients who had sustained traumatic brain injuries. Of those still in vegetative state 1 month after injury, 52% went on to recover consciousness by 1 year posttrauma. Of those still in vegetative state at 3 months following traumatic brain injury, 35% recovered consciousness by 1 year. The likelihood of recovery by 1 year postinjury fell to 16% for those who were still vegetative at 6 months.

The Multi-Society Task Force on PVS[32] also examined the available outcome data for 169 adult patients who remained in vegetative state at 1 month after nontraumatic brain injuries, such as anoxia. Of those still in vegetative state 30 days after a nontraumatic brain injury, the chance of recovering consciousness at 1 year was only 15%. Among those still in vegetative state at 3 months postinsult, only 7% improved by 1 year. No patient who remained vegetative at 6 months recovered consciousness by 1 year.

Given the decreasing probability of recovery from vegetative state of increasing duration and the difference in prognosis associated with the cause of vegetative state (traumatic versus nontraumatic), the Multi-Society Task Force on PVS[33] suggested that the adjective *permanent* be applied to the term vegetative state 12 months after traumatic brain injury and 3 months after nontraumatic brain injury. The term *persistent* is applied when the duration of vegetative state exceeds 30 days.[33] However, the use of the terms *persistent vegetative state* and *permanent vegetative state* is the subject of some controversy as a result of rare cases of late recovery. The Aspen Group has proposed that the terminology *vegetative state* be used, accompanied by its duration and cause(s).[34]

Prognosis for recovery from vegetative state corresponds not only to the duration and cause of vegetative state but also to age (with older patients having a poorer prognosis) and initial Glasgow Coma Scale score and likely corresponds to the findings on imaging studies discussed in the preceding sections of this chapter.

However, it should be noted that the Multi-Society Task Force on PVS performed a retrospective analysis in 1994, long before the diagnostic criteria of MCS were defined and in widespread use. Thus, it is likely that the 434 patient studies included those in vegetative state as well as MCS. Giacino and Kalmar[35] documented that 50% of MCS patients progress to moderate or no disability 1 year after injury compared to less than 5% of vegetative patients. Outcomes are best when patients recover to MCS within 8 weeks of injury. Late recovery (more than 3 months postinjury) is more likely in MCS than vegetative state. Up to 30% of patients in MCS for 1 year can emerge from this condition although typically most are left severely disabled.[36] Clearly, additional research is warranted to better define prognosis based on etiology, age, diagnosis, duration of unconsciousness, neuroanatomical lesions, and functional neuroimaging.

ENHANCING THE POTENTIAL FOR RECOVERY FROM VEGETATIVE STATE AND MCS

Establish a baseline of neurologic function

The patient's medical history must be thoroughly reviewed, and careful serial examinations must be undertaken to document a neurologic baseline. Giacino et al.[37] have outlined a thoughtful approach to the assessment of the patient with a disorder of consciousness.

The assessment of arousal and cognitive content is but a part of a complete physical and neurologic examination. Cranial nerves should be evaluated because their function is a reflection of brain stem integrity. Muscle tone and abnormal posturing should be assessed. Severe spasticity or rigidity may preclude visible limb movement. In patients with disorders of consciousness, strength is inferred from observed spontaneous movement because formal manual muscle testing is not possible. Be aware of contractures that may limit movement. The patient's response to noxious stimulation should be assessed, and reflexes (normal and pathologic) should be noted.

When establishing a baseline of cognitive function, some general principals should be observed. All evaluations should be conducted in an environment free of competing stimuli. A period of observation at the outset of the evaluation is warranted to determine the frequency of spontaneous nonpurposeful movement prior to evaluating the patient's ability to respond. Commands should be short, clear, and given at a time of day when the patient is typically most alert. Requests should target responses that are within the patient's available motor repertoire. Sufficient time should be allowed for an individual with slowed central processing to respond. Eye blinks are notoriously difficult to interpret because the average individual blinks spontaneously more than five times per minute. To optimize the chances of command-following, requests should be repeated, and one may wish to add visual demonstration to verbal requests. If it is difficult to determine whether an observed motor response is random, a simple command such as "stop moving" or "keep still" can be given. Problems such as aphasia and/or limited cognitive endurance should be considered.

Most patients with disorders of consciousness will saturate relatively quickly, and prolonged examinations are unlikely to elicit a patient's best performance.

Multistep instructions, which may include if/then and yes/no components, are significantly more difficult for patients to understand than simple one-step commands. During the early stages of recovery, patients generally have severe memory deficits, including impairments in working memory. When if/then requests are made, the patient may be unable to hold the first part of the command in working memory. As a result, they may follow the instruction given at the end of the sentence. For example, when asked, "If you are a man, then raise one finger," the female patient may proceed to move the designated body part, unrelated to any if/then or yes/no communicative intent. When assessing an individual's ability to respond to yes/no questions, it is essential to select simple questions to which the clinician knows the answer and questions that do not rely on the patient's impaired short-term memory.

When attempting to determine whether a patient has emerged from vegetative state, one should keep in mind that the first signs of recovery include the appearance of sustained visual fixation and tracking as well as localization to auditory or tactile stimuli.[4] Thus, these are the goal behaviors for individuals in vegetative state. An examination targeting more complex behaviors may overlook these important emerging signs of meaningful interaction.

Standardized rating scales should be used to assist in the evaluation of patients with disorders of consciousness. The Western Neuro Sensory Stimulation Profile (WNSSP), the JFK Coma Recovery Scale–Revised (CRS-R), and the Coma/Near-Coma Scale (C/NC) have all been used with some success.[7,38–40] However, the CRS-R appears to be the most sensitive standardized assessment tool that evaluates patients across multiple domains (auditory, visual, motor, oromotor, and cognitive-linguistic function) and incorporates the criteria needed to differentiate vegetative state from MCS and from MCS-emerged.[41,42]

Rule out treatable causes of failure to improve

Before considering the off-label prescription of activating medication, the physician should rule out treatable causes of the patient's failure to improve. This workup should include a noncontrast CT scan of the brain, neuroendocrine screening, an EEG, basic laboratory testing for the causes of dementia, an assessment of the patient's general nutrition, review of medications, and an evaluation of the patient's sleep habits to diagnose possible disruptions in restorative sleep.

INTRACRANIAL COMPLICATIONS

Intracranial complications can impede recovery. A noncontrast CT brain scan is the screening test of choice to rule out the delayed development of complications such as hydrocephalus. Ventricular dilatation occurs in a large percentage of patients after severe brain injury as the result of cerebral atrophy, hydrocephalus, or both. Hydrocephalus can, therefore, present a diagnostic challenge, especially when it is superimposed on severe brain injury with some degree of associated encephalomalacia. In the awake and alert patient, the classic triad of dementia, ataxia of gait, and incontinence may be readily apparent. However, patients who are vegetative or minimally conscious are more difficult to evaluate. The physician should maintain a high index of suspicion in patients who have risk factors for the development of hydrocephalus, including a history of subarachnoid hemorrhage, intraventricular extension of blood, skull fractures (especially depressed skull fractures), and meningitis.[43] Hydrocephalus is generally treated with surgical placement of a ventriculoperitoneal shunt. In uncertain cases, a confirmatory test, such as a cisternogram or lumbar tap tests may be considered.[44] However, no single test or combination of tests has proven to be entirely accurate in predicting shunt responsiveness. Untreated, hydrocephalus will cause progressive neurologic decline in awake and alert patients. In vegetative patients, untreated hydrocephalus can preclude neurologic recovery. In those patients who fail to improve following shunt placement, follow-up CT brain scans or a nuclear medicine shunt study can rule out suboptimal shunt function.

ENDOCRINE DYSFUNCTION

Endocrine dysfunction is also associated with traumatic brain injury. Kelly et al.[45] found that approximately 40% of patients with moderate or severe head injuries suffered posttraumatic pituitary hormonal insufficiency. The sodium and water abnormalities associated with posterior pituitary dysfunction (diabetes insipidus and syndrome of inappropriate antidiuretic hormone) are typically readily apparent to the general practitioner. However, the signs and symptoms of anterior pituitary dysfunction are frequently masked by the patient's neurologic deficits. Therefore, screening should include morning serum cortisol, free T3, free T4, thyroid-stimulating hormone (TSH), insulin-like growth factor I (IGF-I), follicle stimulating hormone (FSH), luteinizing hormone (LH), testosterone (in men) or estradiol (in women), and prolactin levels. Because IGF-1 may lack adequate sensitivity, a provocative test, such as an arginine infusion, may be warranted. If any levels are abnormal or there is a high index of suspicion, the patient may be referred to an endocrinologist for further evaluation. Outcome may be optimized by the identification and treatment of pituitary dysfunction.[46]

SUBCLINICAL SEIZURE ACTIVITY

Subclinical seizure activity can preclude emergence from vegetative state. Seizures and nonconvulsive status epilepticus can be diagnosed electroencephalographically. After EEG confirmation, anticonvulsant treatment should be provided. Elimination of previously unrecognized ongoing seizure activity might markedly improve an individual's level of arousal and attention.

LABORATORY TESTING

Laboratory testing to screen for the abnormalities associated with reversible dementias may be useful. These tests include a B12 level, folate level, rapid plasma reagin (RPR), and TSH. In the presence of abnormal liver function, one may consider checking a serum ammonia level, serum copper level, and ceruloplasmin. For the most part, these dementias are easy to diagnose and treat. Left untreated, however, they can negatively affect an individual's ability to improve neurologically.

MALNUTRITION

Malnutrition and an associated catabolic state may render patients less able to demonstrate robust neurologic recovery. Many patients with disorders of consciousness present to rehabilitation hospitals or long-term care facilities with a history of significant weight loss and laboratory indices consistent with malnutrition. Attention to adequate nutrition is a basic tenet of the care of the brain-injured patient.

SLEEP DISTURBANCE

Sleep is closely linked to brain function. Mounting evidence supports the role of sleep in learning, memory, and neural plasticity.[47–50] Efforts should be made to normalize disturbed sleep–wake cycles. In addition, adequate time for restorative naps during the day should be scheduled.

Eliminate or reduce sedating medications

Pharmacologic intervention should first focus on identifying and reducing or eliminating potentially sedating medication when possible. In a classic study by Temkin et al.,[51] the prescription of anticonvulsant therapy provided no reduction in the incidence of posttraumatic seizures beyond the first 7 days following acute severe head trauma. When continued anticonvulsant therapy is necessary, several issues warrant consideration. Trimble and Thompson[52,53] have demonstrated that anticonvulsant drug selection, blood levels, and combination drug therapy (polytherapy) have an effect on cognitive function. Higher drug levels, even within the therapeutic range, are associated with an increased incidence of adverse cognitive effects. Polytherapy is generally associated with greater impairment on neuropsychological testing than monotherapy.

Of the older anticonvulsant drugs, phenytoin (Dilantin) may have a larger negative effect on cognition than valproic acid (Depakote, Depakene). Among the newer generation of anticonvulsants, evidence points to greater cognitive impairment with topiramate (Topamax) and zonisamide (Zonegran).[54–56] Gualtieri and Johnson[57] examined the differential cognitive effects of carbamazepine (Tegretol), oxcarbazepine (Trileptal), lamotrigine (Lamictal), topiramate, and valproic acid in 159 patients with bipolar disorder. Lamotrigine and oxcarbazepine were found to have the least negative effect on cognition. In a separate study, levetiracetam (Keppra) was found to have no effect on neuropsychological test performance across several cognitive domains in patients with focal epilepsy.[58]

In an uncontrolled preliminary study of the effect of lamotrigine on recovery from severe traumatic brain injury, 13 patients who remained at Rancho Los Amigos levels I to III for an average of 87.5 days after injury were switched from another anticonvulsant to lamotrigine.[59] Compared with the rehabilitation unit's general experience with similar patients, a trend toward improved outcomes, as evidenced by a greater percentage of home discharges, was observed. Given the small size of the study, lack of a control group, and treatment during a phase of spontaneous neurologic recovery, no firm conclusions can be drawn about the effect of switching to lamotrigine for facilitation of recovery.

Animal studies have demonstrated that a number of drugs may exert a positive or negative influence on the recovery of function following brain injury or stroke.[60–62] In a seminal study by Feeney et al.,[63] a single dose of d-amphetamine (which increases levels of the neurotransmitters norepinephrine and dopamine) was given 24 hours after unilateral motor cortex ablation in the rat. When coupled with the opportunity for training, a measurable and enduring improvement in motor recovery was documented compared with injured control animals that did not receive d-amphetamine. Interestingly, animals that received a single dose of d-amphetamine but were restrained in cages too small to allow significant locomotion did not show this facilitation of motor recovery. The investigators also found that the administration of a single dose of the dopamine receptor blocker haloperidol within 24 hours of unilateral motor cortex injury markedly slowed recovery of motor skills in the rat even if an opportunity for training was allowed. This study elegantly demonstrates that medications can facilitate or inhibit motor recovery.

Goldstein[62] makes the case that drugs that affect neurotransmitter systems may modulate neural plasticity and recovery from traumatic brain injury. The weight of available experimental evidence supports avoiding medications that are dopamine or norepinephrine antagonists. This includes neuroleptics, metoclopramide (Reglan), and prochlorperazine (Compazine). Neuroleptic medications may prolong the period of posttraumatic amnesia.[64,65] Prazosin (Minipress) and terazosin (Hytrin) may inhibit noradrenergic neurotransmission via selective blocking of alpha-1 receptors. The alpha-2 selective adrenergic receptor agonist clonidine (Catapres) has been found to inhibit motor recovery in animal models when given acutely after injury.[62] This alpha-2 agonist suppresses the release of norepinephrine from postganglionic sympathetic nerves. The reader is referred to Chapter 16 for a detailed discussion of commonly used medications and their effects on neurotransmitter systems.

PHARMACOLOGIC INTERVENTION TO ENHANCE AROUSAL AND RESPONSIVENESS

Medications that are prescribed to facilitate recovery from vegetative state and MCS are thought to exert their effects

through the modulation of neurotransmitter systems. Our understanding of these systems is still evolving. Clearly, pharmacologic intervention may be beneficial in the treatment of individuals with disorders of consciousness. The drugs used to facilitate neurologic recovery in these patients are generally well-known medications that are used off-label. A discussion of herbal medications is outside the scope of this chapter.

Off-label prescribing is the physician practice of prescribing a drug for a purpose different from that for which it is approved by the Food and Drug Administration (FDA). It should be noted that the prescription of each of the medications to be discussed here for brain injury-induced disorders of consciousness is considered off-label. Legally, any approved product may be used for purposes other than that for which it has received FDA approval.[66] In other words, off-label prescribing is not illegal. Because there are no approved drugs for the treatment of certain diseases, such as disorders of consciousness, and because the discovery of novel therapeutic applications of existing medications proceeds faster than the historically slow FDA review process, off-label use may reflect state-of-the-art treatment or even the standard of care. Physicians may wish to inform patients or their representatives of the intent to use a medication off-label.[67] As with all informed consent, the risks and benefits of both the proposed treatment and its alternatives should be discussed. If the intent of drug treatment is to provide potential patient benefit, it is not considered experimental, and therefore, approval of an institutional review board is not necessary. If, on the other hand, the drug is being prescribed to test a theory, then the intervention should be considered an experiment, and institutional review board approval is recommended.

The rationale for neurotransmitter augmentation relates to known disturbances in neurotransmitter systems following brain injury. Immediately following brain trauma, acute neuroexcitation releases neurotransmitters, and the measured levels of glutamate, dopamine, norepinephrine, and acetylcholine are elevated. However, during the chronic phase, beginning more than 24 hours after injury and lasting for weeks to months, these neurotransmitter systems may be functionally depressed.[61] In theory, pharmacologic intervention may be able to normalize the equilibrium of neurotransmitter systems that have been altered by trauma.

Arciniegas and Silver[68] proposed that medication choices should be based on the hypothesized link between the neurotransmitter systems and the targeted cognitive process. Thus, posttraumatic impairments in arousal would be expected to be sensitive to catecholaminergic, cholinergic, histaminergic, and/or glutaminergic augmentation.

Catecholaminergic neuromodulation

Dopamine and norepinephrine both fall under the category of catecholamine neurotransmitters. Each has been studied in the context of improving cognitive function after brain injury. Dopaminergic neurons are found in the hypothalamus and the substantia nigra of the midbrain whereas noradrenergic neurons are primarily located in the locus ceruleus and lateral tegmentum of the brain stem. These neurons contribute to the ARAS and have been implicated in the maintenance of arousal and attention.

DOPAMINERGIC NEUROMODULATION

Amantadine hydrochloride

Originally designed as an antiviral medication, amantadine (Symmetrel) has been explored as an agent to facilitate recovery following severe traumatic brain injury. Amantadine enhances dopaminergic neurotransmission both pre- and postsynaptically. It facilitates dopamine release and blocks its reuptake presynaptically. Amantadine also increases the number of postsynaptic dopaminergic receptors and potentially alters their configuration. In addition, amantadine may help restore the balance between glutaminergic and dopaminergic neurotransmitter systems through its role as an N-methyl-D-aspartate (NMDA) antagonist. The NMDA receptor is one of several glutamate receptors.

Giacino et al.[69] conducted a well-designed, randomized control study of amantadine's effect on the rate of recovery of 184 patients in either vegetative state or MCS. All patients were 1 to 4 months posttraumatic brain injury and were enrolled in inpatient rehabilitation. Patients were randomly assigned amantadine or placebo for 4 weeks, and they were followed for an additional 2 weeks after treatment was terminated. The Disability Rating Scale (DRS) was used to assess each patient's clinical status. Recovery was measurably faster in the amantadine group during the 4-week treatment period regardless of whether patients were enrolled early (28–70 days postinjury) or late (71–112 days postinjury) or whether they were in vegetative state or MCS at the start of the study. However, the rate of recovery slowed considerably during the amantadine washout period. At 6-week follow-up, the change in DRS scores between baseline and week 6 was indistinguishable in the two groups.

In a single case design study by Zafonte et al.,[70] amantadine was prescribed to a 36-year-old male 5 months following a traumatic brain injury. His initial Glasgow Coma Scale score was III. His best performance prior to drug administration included only visual fixation and tracking. The dose of amantadine was gradually increased to 400 mg per day. Neurologic improvements were subsequently noted, including command following. When the amantadine dose was reduced, a sharp deterioration in the patient's level of functioning was observed. With reinstitution of amantadine at a total daily dose of 400 mg, the patient went on to make significant progress in his rehabilitation program. He ultimately became independent in basic self-care and ambulation using a cane. Eight months after the injury, amantadine was discontinued, and the patient maintained his neurologic gains. Thus, the authors suggest that amantadine may have a role in the treatment of patients in MCS.

In an 8-week, prospective, double-blind, randomized trial, Patrick et al.[71] assessed the effectiveness of the

dopamine agonists amantadine and pramipexole (Mirapex) on the neurologic recovery of 10 children and adolescents who were at or below a Rancho Los Amigos level of III for at least 1 month following traumatic brain injury. The mean age of study participants was 16.7 years. Six of the 10 children were prescribed amantadine, and four were prescribed pramipexole. Overall, the weekly rate of change as measured with the C/NC, WNSSP, and DRS was significantly better for those children who were prescribed a dopamine agonist medication than those who were not. No significant difference in efficacy was seen between the two drugs.

Reynolds et al.[72] studied 588 patients who sustained anoxic brain injuries. Methylphenidate was given to eight patients: Six received amantadine, and two received both. The patients receiving neurostimulants trended toward improved command-following and survival to hospital discharge.

Kraus et al.[73] evaluated the effect of amantadine in 22 traumatically brain-injured adults, the majority of whom were more than 1 year postinjury. The investigators hypothesized that amantadine would exert its effect in the prefrontal cortex. Neuropsychological testing demonstrated significant improvements in executive function, and analysis of PET data revealed a corresponding measurable increase in left prefrontal cortex glucose utilization.

Amantadine is approved for use in the prophylaxis and treatment of infection caused by various strains of influenza A virus. Amantadine is also used to treat Parkinsonism and drug-induced extrapyramidal reactions. Its use for disorders of consciousness associated with brain injury is considered off-label.

Peak plasma concentration is achieved between 2 and 4 hours after oral administration. The half-life of amantadine averages 15 hours in young patients and 29 hours in the elderly. Amantadine generally exerts its effect within 4 weeks of administration.

The most common adverse effects associated with amantadine are nausea, dizziness, and insomnia. Because patients with disorders of consciousness are unable to complain of nausea, it is prudent to monitor gastric residuals in those individuals on tube feeding. If gastric residuals exceed 70 to 100 mL, the dose should be decreased or the drug should be discontinued to reduce the risk of emesis and aspiration. Less frequently reported are depression, anxiety, irritability, confusion, anorexia, dry mouth, constipation, diarrhea, ataxia, tachycardia, diaphoresis, hypertonicity, orthostatic hypotension, peripheral edema, headache, somnolence, lability, and fatigue. Instances of tachycardia, diaphoresis, and hypertonicity in patients with disorders of consciousness can be confused with sympathetic storming, warranting a reduction or tapering off the drug. Reversible liver enzyme abnormalities have also been reported in patients receiving amantadine. It may cause mydriasis and should not be given to patients with untreated angle closure glaucoma. Furthermore, amantadine should not be discontinued abruptly because of the possibility of triggering neuroleptic malignant syndrome, especially if the patient is receiving neuroleptics concurrently. When given with triamterene/hydrochlorthiazide (Dyazide), an increase in blood levels of amantadine may occur, increasing the likelihood of adverse effects. Because of the possibility of adverse cardiac effects, it may be prudent to obtain an electrocardiogram (EKG) prior to the initiation of amantadine and to check a follow-up EKG a few days into treatment.

Adult dosing may start at 50 mg once daily. The dose can be increased to a maximum of 400 mg per day, generally given in divided doses of 200 mg twice daily. An improvement in arousal may be apparent at doses of 100 mg twice daily. The dose should be markedly reduced in patients with renal disease. Amantadine is excreted in the urine, and clearance of amantadine is significantly decreased in patients with renal insufficiency. The elimination half-life increases two- to threefold when the creatinine clearance is reduced. In patients on hemodialysis, clearance of amantadine averages 8 days, and a lower dose should be given only one to two times per week.

Sinemet

A preparation of carbidopa and levodopa (Sinemet) increases dopamine synthesis presynaptically. In 1988, Lal et al.[74] explored the use of Sinemet for 12 patients who had sustained either traumatic brain injuries or hypoxic ischemic brain injuries. Sinemet was found to exert a favorable effect on measures of alertness, memory, posture, and speech.

Patrick et al.[75] studied 10 children (mean age 13.7 years) who were 30 days or more posttraumatic brain injury. One of a variety of dopaminergic agents (either methylphenidate, pramipexole, amantadine, bromocriptine, or levodopa) was prescribed. The slope of the patients' premedication recovery curve was used for comparison against the rate of change observed on medication. A trend toward greater improvement over time was documented, using the WNSSP, when the children were prescribed a dopaminergic drug. The authors concluded that dopamine-enhancing medications may accelerate recovery in children with reduced responsiveness. This small study was undertaken during the period of spontaneous recovery within the first 3 to 4 months postinjury, making generalization of these results difficult.

Matsuda et al.[76] subsequently investigated the effect of dopaminergic augmentation in three patients who remained in persistent vegetative state after traumatic brain injury. All three patients had MRI evidence of high-intensity lesions within the dopaminergic pathway of the dorsolateral midbrain. In addition, all three exhibited physical findings consistent with Parkinsonism, including rigidity, akinesia, and/or tremor. Rapid recovery within 1 to 4 weeks after initiation of Sinemet was seen in all patients.

Case 1 was a 14-year-old boy who had sustained a traumatic brain injury with an initial Glasgow Coma Scale score of IV. He remained in vegetative state at 3 months postinjury at which point benserazide/levodopa 25/100 mg twice daily was prescribed. Nine days later, he began to localize by

turning his eyes toward voices. Twenty days after the initiation of levodopa, he was able to follow commands. One year later, he was able to walk to high school independently, and the medication was discontinued.

Case 2 was a 27-year-old man who had suffered a traumatic brain injury with an initial Glasgow Coma Scale score of IV. He remained in vegetative state at 1 year postinjury at which time levodopa was prescribed. Eight days later, he began to show evidence of visual tracking. Twenty-five days later, the medication was changed to benserazide/levodopa. At that point, he began to communicate yes and no via eye blinks. Ten months after the start of the medication (22 months after his injury), he began to use a word processor to communicate. One year after the drug was started, he was able to write, "I want to eat sushi and drink beer!"

Case 3 was a 51-year-old gentleman with posttraumatic brain injury with an initial Glasgow Coma Scale score of VI. Seven months after trauma, he remained in vegetative state. It was at this time that carbidopa/levodopa was initiated in a dose of 10/100 mg three times daily. Four days after start of treatment, he was able to follow simple verbal commands for the first time. Two months after the medication was started, his tracheostomy tube was weaned, and he was able to speak and state his name and address correctly.

The authors concluded that levodopa treatment should be considered for patients with signs of Parkinsonism and MRI findings of lesions in the dopaminergic pathways from the substantia nigra or tegmentum of the brain stem.

Levodopa works presynaptically and, therefore, requires relatively intact dopaminergic neurons to exert its effect. Matsuda et al.[77] contended that one should select a specific dopaminergic agent based on whether the drug acts presynaptically or postsynaptically, using neuroimaging studies to help guide drug selection. For example, if there is only incomplete damage to the substantia nigra or tegmentum, levodopa may be effective. In the absence of contraindications, this drug is a reasonable choice to facilitate neurologic recovery in patients who have plateaued in vegetative or MCS.

When levodopa is administered alone, it is rapidly decarboxylated in the peripheral tissue so that only a small portion is left to cross the blood-brain barrier. The addition of carbidopa inhibits the inactivation of peripheral levodopa. Sinemet, which is a combination of levodopa and carbidopa, is FDA-approved for use in Parkinson's disease and Parkinsonian syndrome. Its use to facilitate improved alertness for brain-injured patients is off-label. The mean time to peak concentration of levodopa after a single dose of Sinemet is 0.5 hour. The plasma half-life of levodopa in the presence of carbidopa is approximately 1.5 hours. Extended-release preparations are available, such as Sinemet CR, which release the drug over a 4- to 6-hour period. Peak concentrations of levodopa are reached approximately 2 hours after a single dose of Sinemet CR 50/200. However, the bioavailability of levodopa from Sinemet CR is not as high as that in Sinemet. Therefore, the total daily dose of levodopa necessary to produce a clinical response is usually higher when using the sustained-release formulation.

Because of the risk of insomnia, it may be preferable to administer Sinemet two to three times per day with the last dose given in the late afternoon. There are no specific guidelines regarding its use in vegetative state and MCS, and there is wide variation in how this drug is prescribed. It is estimated that 70 to 100 mg daily of carbidopa is necessary to saturate peripheral dopa decarboxylase. Therefore, patients who are receiving less than this amount of carbidopa may be more likely to experience nausea and vomiting. Upward titration of the dose should proceed carefully while observing for the possibility of side effects. Because patients with disorders of consciousness are unable to communicate that they are nauseated, gastric residuals should be carefully checked. If gastric residuals consistently exceed 70 to 100 mL, the dose should be decreased and/or a preparation with more carbidopa should be considered, i.e., changing from a single 25/250 (25 mg of carbidopa and 250 mg of levodopa) tablet to two tablets of 25/100 each.

Sinemet should be administered cautiously to patients with a history of myocardial infarct and/or atrial, nodal, or ventricular arrhythmias. Because of the possibility of adverse cardiac effects, it may be prudent to obtain an EKG prior to the initiation of Sinemet and to check a follow-up EKG a few days into treatment. Malignant melanoma and narrow-angle glaucoma are contraindications to use of this drug. Sinemet may also increase the possibility of an upper gastrointestinal hemorrhage in patients with a history of peptic ulcer disease. The most common adverse reactions seen with Sinemet are nausea, dyskinesias, and other involuntary movements. Psychosis may be seen in high-level patients on rare occasion. Neuroleptic malignant syndrome has been reported in association with rapid dose reductions or withdrawal of Sinemet. Sinemet should not be used with nonselective monoamine oxidase (MAO) inhibitors. Orthostatic hypotension may be observed when Sinemet is added to a drug regimen including antihypertensive medication, and adjustment of the dose of the antihypertensive drug or drugs may be necessary. The concomitant use of tricyclic antidepressants and Sinemet may rarely cause hypertension and dyskinesia.

Drugs that are dopamine receptor antagonists may reduce the effectiveness of Sinemet. Although Reglan may improve gastric emptying and thus increase bioavailability of Sinemet, its action as a dopamine receptor antagonist may adversely affect Sinemet's therapeutic efficacy.

Bromocriptine

Bromocriptine (Parlodel) is a nonselective dopamine receptor agonist that works postsynaptically primarily at D2 and less so at D1 receptor sites. Bromocriptine may have an advantage over other dopaminergic drugs that work presynaptically in that it does not rely on intact dopaminergic neurons. Bromocriptine affects dopamine receptor sites directly. Therefore, if dopaminergic neurons are so severely damaged that no amount of presynaptic activation

will result in sufficient dopamine release across the synaptic junction, then a direct dopamine agonist such as bromocriptine should be considered.

In a small study evaluating the effect of bromocriptine on recovery from vegetative state, Passler and Riggs[78] found that five adult patients who were in vegetative state for more than 30 days showed greater recovery of physical and cognitive function compared with patients described in previous outcome studies reported in the literature. However, the small sample size and the prescription of medication during a time of spontaneous recovery prohibit drawing firm conclusions from this study.

A double-blind, placebo-controlled, crossover design study with 24 high-level patients demonstrated that bromocriptine improved performance on tasks of executive function subserved by the prefrontal region, but it had no effect or a negative effect on working memory.[79] The effect of bromocriptine on working memory was subsequently evaluated by Gibbs and D'Esposito[80] using fMRI. Decreased activity during memory encoding was observed, suggesting that excess dopaminergic stimulation may result in impaired working memory encoding.

Bromocriptine is approved for use in the treatment of Parkinson's disease, hyperprolactinemia, and acromegaly. Its prescription for disorders of consciousness following brain injury is considered off-label use. Bromocriptine is generally started at 2.5 mg once daily. The dose can be increased gradually every few days as tolerated until an optimal response is seen. Adverse effects are more likely if the dose exceeds 20 mg daily.

Contraindications to the prescription of bromocriptine include uncontrolled hypertension and sensitivity to any ergot alkaloid. Use in pregnancy or in the postpartum period is not recommended.

As with Sinemet, bromocriptine should be prescribed with caution to patients with a history of myocardial infarct and/or atrial, nodal, or ventricular arrhythmia. Because of the possibility of adverse cardiac effects, it may be prudent to obtain an EKG prior to the initiation of bromocriptine and to check a follow-up EKG a few days into treatment.

Adverse reactions include nausea, headache, dizziness, vomiting, fatigue, hypotension, and insomnia. The incidence of adverse effects is highest at the beginning of treatment and, as noted, with doses in excess of 20 mg daily. Blood pressure should be monitored closely during the first few days of drug administration.

Apomorphine

Apomorphine is a nonselective dopamine agonist that also activates serotonin receptors and alpha-adrenergic receptors. It is most commonly used in advanced Parkinson's disease when levodopa and other dopamine agonists fail. Emesis is a common side effect, and in veterinary medicine, it is used to induce vomiting in dogs that have ingested poisons. Fridman et al.[81] studied eight patients in vegetative state or MCS of 1 to 4 months duration after severe traumatic brain injury in an open label pilot study using continuous subcutaneous apomorphine infusion. Improvements were seen as quickly as within 24 hours up to as late as 4 weeks. However, the study was performed within a time frame during which spontaneous recovery could still be expected, and no control group was used for comparison.

Combination dopaminergic therapy

Kraus and Maki[82] assessed combined amantadine and carbidopa/levodopa therapy in the treatment of a 50-year-old female with frontal lobe syndrome 5 years after her traumatic brain injury. Treatment with amantadine reduced some but not all of her symptoms. The addition of carbidopa/levodopa resulted in significant additional improvements. The robust effect of combined dopaminergic treatment was attributed to the differential effect of each agent on pre- and postsynaptic dopaminergic activity as well as on the role of amantadine as an NMDA glutamate receptor antagonist. These findings may have implications for the use of combination therapy in patients with disorders of consciousness.

The combination of amantadine and Sinemet can be powerful in improving the alertness of patients with disorders of consciousness (pers. obs.). However, more research is needed before any specific treatment regimen can be recommended.

Noradrenergic neuromodulation

Stimulants such as methylphenidate (Ritalin), amphetamines (Dexedrine and Adderall), and atomoxetine (Strattera) have effects on arousal, attention, processing speed, distractibility, memory, and mood in healthy people. Therefore, their usefulness in the treatment of the cognitive deficits seen after brain injury has been the subject of much interest. However, their potential for exacerbating the tachycardia so frequently seen in the acute stages of recovery following brain injury may limit the patient's ability to tolerate these drugs. In addition, tricyclic antidepressants, which modulate several neurotransmitters, including norepinephrine, have been explored as potential beneficial agents in the treatment of brain injury.

METHYLPHENIDATE

Methylphenidate (Ritalin) works presynaptically to increase the release of both dopamine and norepinephrine, thereby facilitating catecholaminergic neurotransmission. Thus, methylphenidate requires relatively intact catecholaminergic neurons in order to exert its presynaptic effect.

Methylphenidate is approved for the treatment of attention deficit hyperactivity disorder (ADHD) and narcolepsy. Its prescription for disorders of consciousness following brain injury is considered off-label.

Plenger et al.[83] studied the effect of methylphenidate on recovery from traumatic brain injury. They concluded that methylphenidate enhanced the rate of recovery but not the ultimate outcome following brain trauma. However, limitations of this study included small sample size, high dropout

rate, and administration of the drug during the period of spontaneous recovery.

In two separate studies by Whyte et al.,[84,85] methylphenidate appeared to improve processing speed in awake and alert brain-injured patients. More recently, Martin and Whyte[86] assessed the effect of methylphenidate on patients in either vegetative state or MCS with disappointing results. In their rigorous single-subject, crossover design trials, methylphenidate had no effect on the level of arousal in either vegetative state or MCS. In addition, no improvement in the accuracy of responses was observed in minimally conscious patients. Thus, the promising results of methylphenidate trials in higher-level patients did not generalize to this patient population. However, the impact of methylphenidate in combination with medication that targets different aspects of neurotransmitter systems has not been systematically studied.

Methylphenidate is generally started at a dose of 5 mg twice daily. The dose can be increased gradually until an optimal response is achieved or intolerance develops. The usual dose prescribed in the rehabilitation setting is between 10 mg and 20 mg twice per day. Peak effect is observed between 30 minutes to 2 hours after drug administration. The duration of drug effect is approximately 3 to 6 hours. Generally, the first tablet is given upon awakening with additional doses given at 4- to 6-hour intervals. To reduce the likelihood of insomnia, drug administration should be avoided in the evening. Longer acting preparations are available.

Adverse effects include insomnia, headache, nervousness, and anorexia. Modest increases in heart rate and blood pressure may be observed. Contraindications to the prescription of methylphenidate include serious structural cardiac abnormalities, cardiomyopathy, coronary heart disease, serious arrhythmias, and glaucoma. Use in pregnant or breast-feeding women and in individuals on MAO inhibitors should be avoided.

AMPHETAMINES

Dextroamphetamine (Dexedrine) and Adderall (a mixture of dextroamphetamine and racemic amphetamine) work presynaptically to increase the levels of both norepinephrine and dopamine. Thus, amphetamines require relatively intact catecholaminergic neurons to exert their effect. In addition, amphetamines inhibit the reuptake of serotonin, increasing available serotonin, a monoamine neurotransmitter that normalizes mood and sleep and reduces nociception. Despite the promising results seen in Feeney's[63] rat model of amphetamine-enhanced motor recovery, no compelling evidence exists that definitively supports the use of amphetamines for disorders of consciousness at this time.

Amphetamines are approved for the treatment of narcolepsy, ADHD, and as a short-term adjunct to calorie restriction and behavior modification for the management of obesity. The prescription of amphetamines for disorders of consciousness following brain injury is considered off-label use.

Amphetamines are typically started at a dose of 5 mg twice per day. The dose may be raised by 5 to 10 mg at weekly intervals until an optimal response is achieved or intolerance develops. The usual adult dose varies between 10 mg and 20 mg twice per day in the rehabilitation setting. Peak effect is observed between 30 and 60 minutes after drug administration. Typically, the first tablet is given upon awakening with additional doses given at 4- to 6-hour intervals. To reduce the likelihood of insomnia, drug administration should be avoided in the evening. Extended-release preparations are available.

Amphetamines are contraindicated in the presence of advanced arteriosclerosis, heart failure, recent myocardial infarction, serious cardiac structural abnormalities, coronary artery disease, cardiac arrhythmias, cardiomyopathy, moderate to severe hypertension, hyperthyroidism, agitated states, glaucoma, and in individuals with known hypersensitivity to sympathomimetic amines. Pregnant or breast-feeding women and individuals on MAO inhibitors should avoid taking amphetamines. Although a history of drug abuse is a relative contraindication, this may be a moot point for patients with disorders of consciousness. Serious cardiovascular effects can be seen if amphetamines are administered with tricyclic antidepressants, resulting from marked increases in the concentration of the amphetamine.

Adverse effects include hypertension, palpitations, tachycardia, dizziness, psychosis, insomnia, dyskinesia, headaches, tremor, dryness of the mouth, anorexia, weight loss, urticaria, and impotence.

ATOMOXETINE

Atomoxetine (Strattera) is a selective norepinephrine reuptake inhibitor that is approved for use in the treatment of ADHD. Atomoxetine may also increase levels of dopamine and acetylcholine. Its prescription for disorders of consciousness following brain injury is considered off-label use.

Murdock and Hamm[87] assessed the effect of atomoxetine given within 24 hours of moderate traumatic brain injury in rats. The investigators found that the atomoxetine-treated animals had measurably less cognitive deficits than saline-treated animals. However, in a separate experiment, it was found that if atomoxetine treatment was delayed for 10 days after brain trauma and provided on days 11 through 29 after injury, the treated animals developed greater cognitive impairment. Therefore, it is clear that the timing of drug administration may influence its potential impact on the central nervous system.[61]

There are no clinical studies evaluating the efficacy of atomoxetine for prolonged disorders of consciousness following traumatic brain injury. However, Ripley[88] asserts that, theoretically, this norepinephrine reuptake inhibitor may be useful if added to agents that affect different aspects of the catecholaminergic neurotransmitter systems.

Strattera should not be taken with an MAO inhibitor or within 2 weeks of discontinuing an MAO inhibitor. Use of Strattera is contraindicated in the presence of narrow-angle

glaucoma. Liver function should be monitored while on Strattera, and dosage adjustment is recommended for patients with liver disease. Uncommon allergic reactions, including angioneurotic edema, urticaria, and rash, have also been reported in patients taking Strattera. Because Strattera can increase blood pressure and heart rate, it should be used with caution in patients with hypertension, tachycardia, or cardiovascular disease. The dose of atomoxetine may need to be reduced when the drug is administered with paroxetine (Paxil), fluoxetine (Prozac), and quinidine.

Adverse events in patients treated with Strattera include dyspepsia, nausea, vomiting, fatigue, reduced appetite, dizziness, orthostatic hypotension, insomnia, urinary retention, and mood swings. Aggression, irritability, somnolence, and vomiting are generally the main reasons for discontinuation of the drug.

TRICYCLIC ANTIDEPRESSANTS

Tricyclic antidepressants, including desipramine (Norpramin), protriptyline (Vivactil), doxepin (Sinequan), imipramine (Tofranil), amitriptyline (Elavil), and nortriptyline (Pamelor), are FDA-approved for the treatment of depression, panic disorder, obsessive-compulsive disorder, ADHD, migraine headaches, eating disorders, and bipolar disorder. Tricyclic antidepressants may affect widespread neurotransmitter systems. These drugs selectively block norepinephrine reuptake, thereby increasing available norepinephrine in the central nervous system. Tricyclic antidepressants may also inhibit the reuptake of serotonin, thereby potentiating its effects. In addition, tricyclic antidepressants exhibit significant anticholinergic and antihistaminergic properties.

Reinhard et al.[89] examined the effects of tricyclic antidepressants in three brain-injured patients. Case 1 was a 27-year-old man in MCS 6 months postinjury. He was started on amitriptyline 50 mg daily, and within several days, he began to verbalize and respond to yes/no questions. By 7 months postinjury, he was able to begin gait training. When the amitriptyline was discontinued, his level of responsiveness deteriorated, and his verbalizations ceased. With reinstatement of the drug, he once again improved.

Case 2 was a 23-year-old woman at a Rancho Los Amigos level III 2 months postinjury. Desipramine was started and gradually increased to a total daily dose of 50 mg. Following administration of the drug, she began to follow commands. Three months later, the desipramine was gradually discontinued, and the patient became lethargic. When the drug was resumed, there was a rapid improvement in her level of alertness and function.

Case 3 was a 26-year-old man who remained in MCS for 19 months. He was prescribed desipramine, 75 mg daily. Four days later, he began to verbalize single words for the first time. Within months, he was able to communicate effectively. When the desipramine was discontinued several months later, there was no deterioration in his level of function. In all three cases, there was a close temporal relationship between the neurologic improvement and the prescription of a tricyclic antidepressant. In two of the three cases, the level of arousal deteriorated when the drug was withdrawn and improved when the drug was resumed, supporting the contention that the tricyclic antidepressant was responsible for the change in neurologic status.

Tricyclic antidepressants may be administered once a day due to their long half-life. Most adverse effects reflect the anticholinergic and central nervous system properties of this class of drugs. Thus, in the population of patients with disorders of consciousness, the primary relevant concerns include urinary retention, gastroesophageal reflux with possible aspiration of stomach contents, and lowering of seizure threshold. Although drowsiness is common, some patients may demonstrate restlessness and insomnia. The presence of glaucoma, cardiovascular disease, and the concomitant administration of MAO inhibitors are contraindications to use of tricyclics.

In addition, drug interactions may be serious. Sympathomimetic medication, such as amphetamines, should not be given with tricyclic antidepressants due to the possibility of fatal pressor and cardiac effects. Coadministration of tricyclics with levodopa may delay gastric emptying of levodopa, allowing for its inactivation. Caution should also be exercised when prescribing tricyclic antidepressants to patients on thyroid medication.

GABA neuromodulation

GABA is a major inhibitory neurotransmitter. Medications such as zolpidem (Ambien), diazepam (Valium), lorazepam (Ativan), and baclofen (Lioresal) facilitate GABA neurotransmission.

ZOLPIDEM (AMBIEN)

Zolpidem facilitates GABA neurotransmission. It is a nonbenzodiazepine hypnotic of the imidazopyridine class. Benzodiazepines bind nonselectively to all omega receptor subtypes of the $GABA_A$ receptor complex. Zolpidem, however, stimulates GABA neurotransmission by selectively binding to only omega 1 receptors.

Clauss and Nel[90] studied the effect of zolpidem on three patients who had been in vegetative state for at least 3 years. Prior to drug administration, the patients' Rancho Los Amigos levels ranged from I to II, and their Glasgow Coma Scale scores were between VI and IX. All three patients regained transient awareness and the ability to follow commands and communicate for up to 4 hours after drug administration. One hour after drug administration, Rancho Los Amigos levels increased to between V and VII, and Glasgow Coma Scale scores ranged from X to XV. It is noteworthy that all of the patients who emerged from vegetative state did so within 1 hour on the first day that the drug was administered. However, all three patients returned to vegetative state daily when the effect of the medication subsided. Clauss and Nel[90] postulated that brain injury triggers a state of dormancy of normal, unaffected brain tissue called diaschisis and that the symptoms exhibited by brain-injured

patients are the result of a combination of structural brain damage as well as neurodormancy. Reversal of diaschisis was proposed to explain the drug effect.

In a separate study of four brain-injured patients, three were found to have poor tracer uptake in the areas of brain damage as well as in undamaged areas of the cerebellum, consistent with cerebellar diaschisis.[91] After zolpidem administration, cerebral perfusion in the areas of brain injury improved measurably, and the cerebellar diaschisis was completely reversed. Zolpidem is thought to exert its effect by binding GABA receptors on neurodormant cells, thereby allowing reversal of diaschisis.

In a prospective open label study, Thonnard et al.[92] assessed the effect of zolpidem in 60 chronic brain injured patients. Of these, 31 had sustained traumatic brain injuries, and 29 had suffered nontraumatic events. At the outset of the trial, 32 were in MCS, and 28 were in vegetative state. Using CRS-R, a total of four of 60 patients demonstrated clinical improvements, but only one (traumatic brain injury in MCS) met the criteria to change diagnostic categories per CRS-R guidelines. Whyte and Myers[93] found that a similar, small percentage of patients responded to zolpidem.

To assess response to zolpidem based on mechanisms of injury, Du et al.[94] studied 127 patients in vegetative state during 1 week of treatment. The authors concluded that zolpidem was more likely to exert a positive impact on level of consciousness in patients without brain stem injuries and that zolpidem-induced improvements in brain function were rapid rather than gradual.

Chatelle et al.[95] assessed changes in regional brain metabolism after zolpidem administration in three patients in postanoxic MCS using 18-F-flurodeoxyglucose positron emission tomography (FDG-PET) while monitoring them clinically with CRS-R. All three patients recovered functional communication after administration of zolpidem with emergence from MCS. FDG-PET data analysis revealed metabolic activation of prefrontal cortices, supporting the mesocircuit hypothesis to explain the drug's effect.[14] Furthermore, the brain areas that showed increased metabolism after zolpidem did not show significant structural lesions, corroborating the theory of cerebral diaschisis.

The GABA hypothesis suggests that drugs, such as zolpidem and baclofen, may partially reverse impaired GABA neurotransmission, allowing for deactivation of the proposed DMN. Deactivation of the DMN is associated with cerebral engagement in task-oriented, goal-directed activity. Pistoia et al.[26] reviewed the proposed mechanisms through which CNS depressants may exert their positive effect on individuals with disorders of consciousness by reversal of diaschisis (diaschisis hypothesis), restoring the normal balance between synaptic excitation and inhibition (GABA impairment hypothesis), and by modulating information overload to the cortex as a result of filter/gating failure.

Zolpidem is available in 5-mg and 10-mg tablets. It has been approved for the short-term treatment of insomnia. Use for disorders of consciousness is considered off-label. The initial dose for adults with disorders of consciousness or patients with hepatic insufficiency is 5 mg. The dose of zolpidem may be increased but should not exceed 10 mg.

Peak concentration is typically achieved within 1 hour of administration. It is short-acting with a half-life of up to 4 hours.

The most common adverse effects are dizziness, drowsiness, and diarrhea.

BENZODIAZEPINES

Benzodiazepines reduce spasticity and suppress seizures with generally negative effects on memory and overall cognition. Nevertheless, there are isolated case reports of recovery from poorly responsive states following administration of Valium. A 45-year-old Wisconsin man, in vegetative state for 8 years, reportedly improved significantly after being injected with Valium for a routine dental procedure.[96] When medicated, he was able to talk and perform complicated mathematical calculations. Benzodiazepines may work by reducing abnormal tone to the point that patients who were previously dominated by severe spasticity can demonstrate volitional movement to command. Alternatively, benzodiazepines may temporarily abort subclinical seizure activity. Referring to cases of very late emergence from vegetative state, Wijdicks[97] raises the question of recovery versus discovery. He suggests that "miracle cases" of late recovery may in fact represent late discovery of existing neurologic function that had previously gone unrecognized.

GLUTAMATERGIC NEUROMODULATION

One of the important excitatory neurotransmitters in the central nervous system is glutamate. Glutamate is synthesized in the brain, and it serves not only as an excitatory amino acid neurotransmitter, but it is also the precursor of GABA. In the hours immediately after traumatic brain injury, glutamate is responsible for some degree of excitotoxic brain damage. Following injury, excess glutamate is associated with increased seizure risk. However, because glutamate is involved in normal cognitive processes, there may be a place for modulation of this neurotransmitter to improve cognitive function in chronic brain injury.

Modafinil

Modafinil (Provigil) is a central nervous system stimulant that is pharmacologically distinct from other stimulants. Modafinil likely exerts its effects through several neurotransmitters, including the catecholaminergic and serotonergic systems. In addition, modafinil may reduce GABA release and increase the release of glutamate.[98]

Lin et al.[99] used immunocytochemistry techniques to differentiate the potential brain neuronal targets for amphetamine, methylphenidate, and modafinil-induced wakefulness in the cat. Amphetamines and methylphenidate administration caused increased activity in widespread

areas of the cortex, including the caudate nucleus and medial frontal cortex. However, cats treated with modafinil demonstrated activity in the anterior hypothalamus, hippocampus, and amygdala. Because of its relatively unique mechanism of action among the activating medications, modafinil may have a place either as a single agent or in combination therapy with other activating drugs if monotherapy is ineffective.

Modafinil treatment of 10 brain-injured outpatients with excessive daytime sleepiness was described by Teitelman.[100] Moderate to marked improvements in subjective feelings of wakefulness and well-being were reported. Formal neuropsychological testing was not performed.

Modafinil is approved for use in narcolepsy, obstructive sleep apnea/hypopnea syndrome, and shift work sleep disorder. Although modafinil has been used in the treatment of states of hypoarousal following brain injury, its use for disorders of consciousness is considered off-label.

Serious rashes have been reported in patients taking modafinil, and this requires prompt discontinuation of the drug. Multiorgan hypersensitivity reactions with diverse signs and symptoms, including fever and rash with other organ system involvement, have been reported. Psychiatric symptoms may develop in association with modafinil and may necessitate discontinuation of the drug. Insomnia has been reported as well. Modafinil has not been evaluated in patients with a recent history of myocardial infarct or unstable angina. Modafinil should not be used in patients with a history of left ventricular hypertrophy or mitral valve prolapse syndrome.

Adverse effects associated with modafinil include headaches, nausea, vomiting, nervousness, rhinitis, diarrhea, back pain, anxiety, insomnia, dizziness, and dyspepsia. Because patients with disorders of consciousness are unable to communicate that they are nauseated, gastric residuals should be carefully checked. If gastric residuals consistently exceed 70 to 100 mL, the dose should be decreased, or the drug should be discontinued to avoid emesis and aspiration.

The recommended dose of modafinil is 200 mg once daily. Although doses have been prescribed up to 400 mg per day, there is no compelling evidence to suggest that a higher dose confers additional benefit. Because the primary route of modafinil elimination is via metabolism through the liver, patients with severe liver disease should receive a reduced dose. Peak plasma concentration occurs roughly 2 to 4 hours after each dose.

Modafinil may affect the elimination of diazepam, propranolol, and phenytoin, necessitating their possible dose reduction. Modafinil may cause increased blood levels of tricyclics in some patients. However, no significant change in pharmacokinetics has been identified when modafinil is prescribed with either amphetamines or methylphenidate.

CHOLINERGIC NEUROMODULATION

Medications that facilitate cholinergic neurotransmission are strongly associated with their impact on arousal and memory, particularly in patients with dementia. Cholinergic neurotransmission has also been found to be partly responsible for some aspects of arousal and attention and may improve signal-to-noise processing in the cortex.[101]

Activation of the thalamus through the cholinergic projections of the ARAS facilitates transmission of sensory input to higher cortical regions. The ventral projections from the brain stem ARAS modulate basal forebrain activation via catecholaminergic, glutaminergic, and cholinergic neurotransmission. In turn, the pathways from the basal forebrain to the cerebral cortex mediate arousal and attention through cholinergic and GABAergic systems. The cholinergic neurons of the forebrain and hippocampus are particularly susceptible to damage during head trauma as a result of their location near the bony prominences of the skull.

After a state of cholinergic hyperactivity seen in acute traumatic brain injury, the chronic phase of recovery is associated with reduced cholinergic activity.[102] Some aspects of brain injury-induced cognitive impairments in attention and memory have been attributed to this posttraumatic disruption of cholinergic function.[103,104]

The drugs most commonly used to increase the concentration of acetylcholine at cholinergic synapses are cholinesterase inhibitors, which reduce the breakdown of acetylcholine. This class of drugs includes donepezil (Aricept), galantamine (Reminyl), rivastigmine (Exelon), and tacrine (Cognex).

Zhang et al.[105] examined the effects of donepezil on memory and attention in 18 brain–injured patients who were able to participate in neuropsychological testing. The mean time since injury was 4.6 months, and the average Glasgow Coma Scale score, measured between 24 and 48 hours of injury, was IX. In a 24-week, randomized, placebo-controlled, double-blind crossover trial, this pilot study demonstrated improved scores on tests of both sustained attention and short-term memory. These improvements were maintained through the final testing, which was performed 14 weeks after the medication had been terminated. The authors hypothesized that this lasting drug effect might be attributable to long-term alteration of the cholinergic system. Khateb et al.[106] studied the effects of donepezil on 10 patients whose head injury had occurred at least 6 months previously. Although the study did not include a control group, significantly improved performance in divided attention, learning, and speed of processing was documented on the drug. Walker et al.[107] retrospectively examined the effects of donepezil during the acute inpatient rehabilitation of 36 patients with moderate-to-severe brain injuries. Patients were enrolled in this study within 90 days of injury. No differences were seen between the treatment group and a matched control group in outcome as measured by the Functional Independence Measure Cognitive Total Score and rehabilitation length of stay. However, there was a trend toward a greater rate of improvement in global cognitive functioning if patients were started on donepezil early during their inpatient rehabilitation program. The authors suggested that perhaps the measurement tools used in this pilot study might have been too crude to detect subtle improvements in cognition. At this time, there are

no controlled studies examining the effect of cholinergic modulation on recovery from vegetative state or MCS.

For the treatment of dementia of the Alzheimer's type, the recommended initial dosage of donepezil is 5 mg daily. The dose may be increased to a maximum of 10 mg daily. As with the other medications reviewed in this chapter, the use of this drug is considered off-label when prescribed for disorders of consciousness.

Cholinesterase inhibitors should be used with caution in patients with bradycardia or cardiac conduction abnormalities and in patients with asthma or obstructive pulmonary disease. Common side effects include nausea, vomiting, diarrhea, fatigue, insomnia, muscle cramping, and anorexia.

HISTAMINERGIC NEUROMODULATION

Histamine, which is synthesized in the hypothalamus, may have a role in maintaining arousal. Supporting this contention are recent animal studies that demonstrate that histidine decarboxylase knockout mice are unable to remain awake when high task vigilance is required.[108] Furthermore, narcoleptic dogs have been found to have a histamine deficiency.[109] The interaction between histaminergic and other neurotransmitter systems is the subject of considerable research at this time.[110] Although no histaminergic agents are available as yet, this neurotransmitter may hold promise for future use in the treatment of disorders of consciousness.

CONCLUSION

The neural construct of consciousness involves overlapping neuronal networks and diverse neurotransmitter systems. How chronic neurotransmitter dysfunction affects receptor sensitivity or produces adaptive changes in other neuronal systems is largely unknown. Augmentation of a single neurotransmitter system may have far-reaching effects on other neurochemical networks.

Patients with disorders of consciousness may have a range of underlying neuroanatomical and neurochemical alterations. Currently, we are closer to identifying the neurotransmitter systems and the structural and functional neural networks that are important in maintaining consciousness. As our ability to detect these unique differences among patients improves, the term *disorders of consciousness* will likely be replaced with more exact diagnoses that reflect the distinct anatomic and neurochemical networks involved. These advances will hopefully allow new and effective therapeutic agents to be developed to improve the lives of brain injury survivors.

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15

Clinical management of pituitary dysfunction after traumatic brain injury

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PATHOPHYSIOLOGY OF TBI-INDUCED PITUITARY DYSFUNCTION

It has been suspected for almost a century that traumatic brain injury (TBI) can produce pituitary dysfunction, but only over the recent years/last decade have we completed prospective studies that document hypothalamic–pituitary axis damage occurs after TBI. Previously, there were only case reports associating pituitary dysfunction with brain injury. In 2000, Benvenga et al.[1] reviewed these case reports, raising the possibility of an association between TBI and pituitary dysfunction. He further noted that endocrine dysfunction can occur more than 10 years after the initial injury and that the injury may not have been substantial enough to require hospitalization or even be remembered by the patient. Similarly, it is only recently that a clear association has emerged between post-TBI neuroendocrine dysfunction and neurobehavioral and quality-of-life impairments, and evidence of TBI as a cause of pituitary deficiency in all age groups keeps growing.[2]

An important aspect of TBI-induced hypopituitarism is the potential impact on brain recovery. It is accepted in the literature[3–7] that the most common neurobehavioral and quality-of-life complaints affecting TBI survivors are memory and concentration deficits, anxiety, depression, fatigue, and loss of emotional well-being. The fact that receptors for pituitary hormones, especially growth hormone (GH) and insulin-like growth factor-1 (IGF-1), are widely present in the brain supports the assumption that they are an integral part of effective brain repair and recovery.[3–7] Receptors for other endogenous hormones are widespread throughout the brain as well. It is yet unproved in any study that acute hormonal deficiencies in humans have a deleterious impact on the neuroprotective and early repair processes that follows TBI. Future studies will address this important possibility.

The exact mechanisms of injury to the pituitary after TBI are not completely understood. In order to discuss the pathophysiology of the pituitary damage, we briefly point out the functional anatomy of the gland. The pituitary gland is seated at the base of the skull within the sella turcica, being tethered to the hypothalamus by the infundibulum. The diaphragma sella separates it from the suprasellar cistern. Both the anterior and the posterior pituitary receive blood supply from the internal carotids. The blood supplied by the long hypophyseal portal veins is fed from the superior hypophyseal arteries and other small branches of the circle of Willis and provides the anterior pituitary gland with 70%–90% of its blood supply. Moreover, the hypothalamic-releasing hormones are carried by this vascular system to the anterior pituitary. The cellular distribution in the pituitary gland supplied by the long hypophyseal veins includes the somatotrophs (located in the lateral wings of the gland) and the gonadotrophs (mostly located in the peripheral parts of the gland). The short hypophyseal portal veins arise from branches of the intracavernous internal carotid artery, the inferior hypophyseal arteries that enter the sella from below the diaphragma sella, and altogether provide less than 30% of its vascular supply, predominantly in the medial portion of the gland. The posterior lobe receives its blood supply through the inferior hypophyseal arterial branches.

The most possible mechanisms of injury are 1) the direct brain injury event itself; 2) the indirect injuries, such as hypoxia or hypotension; 3) the transient effect of critical

illness or the "stress response;" and 4) the effects of different medications given during the initial critical period after injury that may have the inadvertent effect of suppressing normal hypothalamic and pituitary function. Direct mechanisms refer to fractures through the skull base and sella turcica as well as the shearing injuries of the pituitary, infundibulum, and/or hypothalamus. Although the risk of injury to the anterior lobe is greatest from a basilar skull fracture, the anterior lobe can be injured by any skull fracture or even by severe brain trauma in the absence of fracture.[8] Fractures of the sella turcica after fatal brain injury are found on autopsy for as many as 20% of cases, depending on whether the petrous temporal bone is included in the statistics.[9] Transection or rupture of the pituitary stalk results in anterior lobe infarction because of disruption of the portal blood supply from the hypothalamus to the anterior pituitary. Therefore, it can be inferred that shearing forces delivered from different angles and with varying forces could impair blood flow through the long hypophyseal portal veins to the peripheral pituitary and cause isolated, multiple, or partial deficiencies of anterior pituitary hormone secretion. Despite recent studies,[10,11] there are still no adequate animal models to confirm this inference, and imaging techniques have not been developed to assess blood flow to the pituitary through the hypophyseal portal veins after TBI. In early 2015, Zheng et al. suggested that pituitary apparent diffusion coefficient using diffusion-weighted imaging may help predict pituitary function in patients with TBI;[12] however, the practicality of such models is yet to be proven.

Indirectly, functional damage at the hypothalamic–pituitary region can be the result of a secondary hypoxic insult. Another possibility is diffuse axonal injury (DAI) caused by acceleration–deceleration along with rotational forces in motor vehicle crashes. DAI is the major pathology in a large percentage of TBI admissions and is the predominant cause of loss of consciousness.[13]

Head trauma presents a substantial risk to pituitary function because of that gland's encasement within the sella turcica, its delicate infundibular hypothalamic structures, and its vulnerable vascular supply (Figure 15.1).[14] Therefore, mechanical compression from injury or pituitary gland swelling may play a part in diffuse vascular injury.[15] The long hypophyseal portal vessels and the pituitary stalk are thought to be particularly vulnerable to mechanical trauma, low cerebral blood flow, brain swelling, and intracranial hypertension. The first study that showed traumatic infarction of the anterior pituitary gland was by Daniel half a century ago in a report on fatal head injuries,[16] and it was seen one decade later in larger studies proved by Ceballos[17] and Kornblum.[18]

Benvenga et al.[1] commented on the peculiar vascularization of the pituitary, noting that the peripheral layer of anterior pituitary cells under the capsule receives arterial blood from the capsule and not from the two systems of portal veins. Therefore, these cells and those in a small area close to the posterior lobe are the only surviving cells in cases of pure anterior lobe necrosis. Interestingly, severed portal vessels can regenerate, which may explain the occasional report of recovery from anterior pituitary insufficiency that is a complication of head trauma.[19]

The pathophysiology of acute hypopituitarism after TBI has not been thoroughly investigated. However, recently, Cohan[20] demonstrated that acute central (pituitary) adrenal insufficiency (AI) was present in a majority of patients with moderate-to-severe TBI, measured by acute cortisol and ACTH levels. Factors that correlated with AI were younger age, lower Glasgow Coma Scale (GCS) scores (trauma severity), and early ischemic insults as well as etomidate use. Metabolic suppressive agents (such as propofol and pentobarbital) or etomidate had a transient and reversible effect on the corticotroph function of the pituitary.

The stress of critical illness has serious effects on the acute functioning of all anterior pituitary hormonal axes. The sick euthyroid syndrome (low TSH, low T3, and high reverse T3) occurs commonly in critically ill patients. The gonadotropic axis is also suppressed with acute lowering of gonadal hormones. As with the gonadotropic axis, the serum testosterone is usually low in critically ill males. More research is clearly needed in this area.

More recently, research revealed new possible mechanisms of injury following TBI; one explanation implicates neuroinflammation, in which a complex interaction between several components and mediators of the innate and adaptive immunity appear to determine the extent of destructive inflammation after TBI.[21] Another emerging theory suggests that autoimmunity plays a role in TBI pathophysiology, pointing toward an association between TBI-induced hypopituitarism and the presence of antihypothalamus antibodies and antipituitary antibodies.[22,23] Further research is needed to better understand these mechanisms, which would help in the development of new and effective therapeutic strategies for this patient population.

Pediatric TBI

According to a Centers for Disease Control (CDC) report, annually in the United States, approximately 475,000 children less than 14 years of age will sustain a TBI. There are 37,000 hospitalizations and more than 2,500 deaths. Yearly, more than 30,000 children are disabled due to a TBI. The CDC has also noted that more than 560,000 children are seen in hospital emergency departments and released. They estimated that, annually, more than 900,000 children have mild TBIs.[24,25]

This clearly impacts their physical, cognitive, and neuropsychological competitiveness. Children are also at risk for lifelong posttraumatic hypopituitarism (PTH), which is known to lead to problems with emotional and physical maturation. An intact hypothalamo-hypophyseal axis is necessary for proper growth and development in children and adolescents. Deficiencies in this axis can lead to decreased libido, hypogonadism, short stature, or arrested and precocious puberty.[26]

Niederland et al. studied 26 children 30.6 ± 8.3 months postinjury against 21 age-matched controls.[27] The average age was 11.47 ± 0.75 years. Eleven of 26 patients with TBI had below

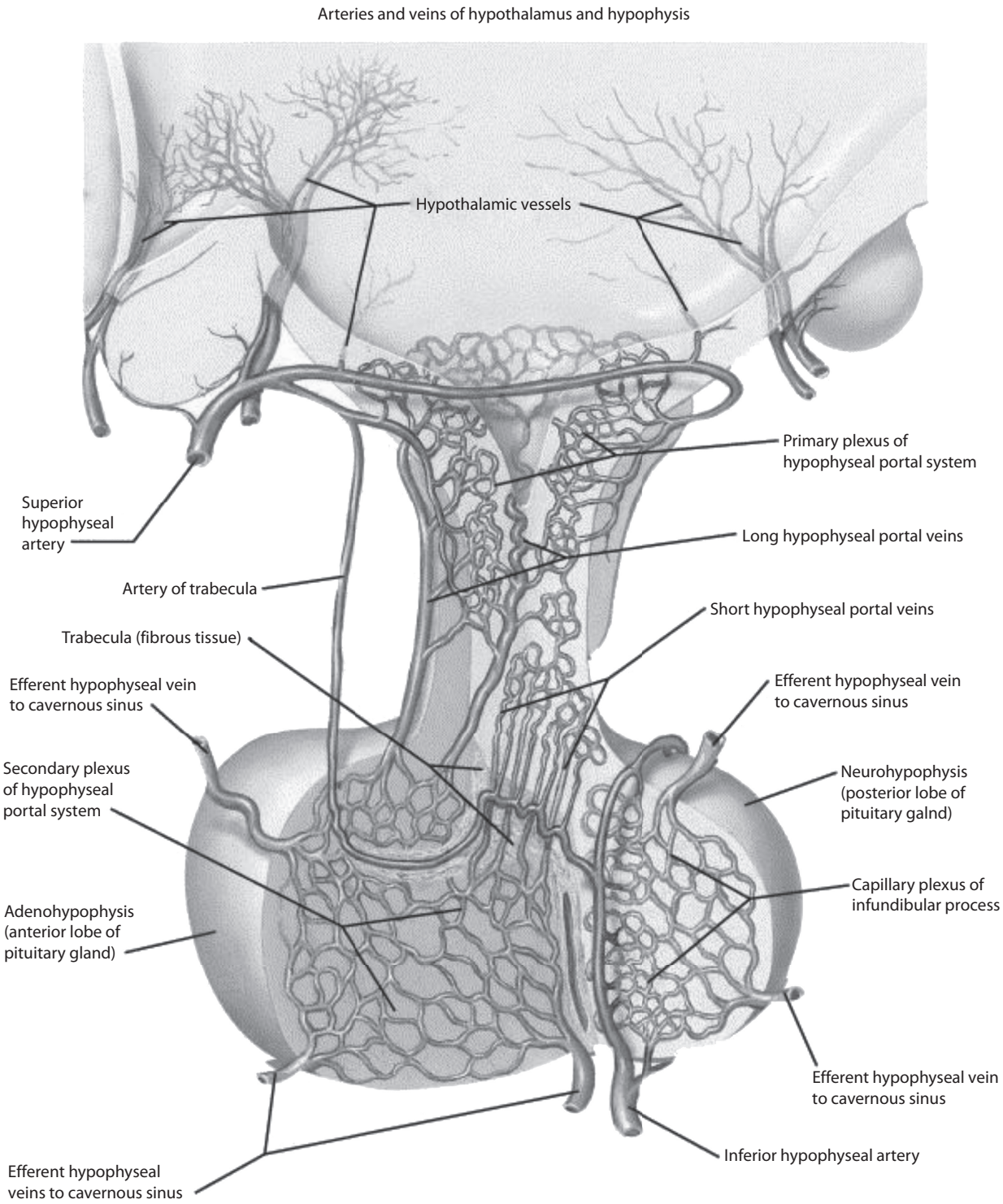

Figure 15.1 Blood supply of the hypothalamus and pituitary. (Reproduced from The Ciba Collection of Medical Illustrations, vol. 4, Library of Congress No. 52-2151, p. 5, Copyright 1965, with permission from Elsevier.)

normal GH responses to two different provocative stimulation tests. Morning basal cortisol levels were below normal in nine patients with TBI. As a group, the GHD subjects were slightly shorter than controls of the same chronological age although the difference was not statistically significant. Although counterintuitive, they found no correlation between the incidence of PTH and the severity of the head injury. This suggests that clinicians cannot discount the possibility of PTH merely because the child did not sustain a severe TBI.

Rose et al. published a literature review on endocrine changes following pediatric TBI.[28] They concluded that PTH in children is common, can evolve over time, and may be permanent. They recommended ongoing endocrine surveillance until at least 1 year postinjury even if the findings

at 6 months were negative. They called for further studies on childhood TBI to better describe the natural progression of endocrine dysfunction.

Acerni also commented on the need for vigilance and awareness of the hormonal complications of a pediatric or adolescent TBI and its contribution to the TBI disease process. "It is not acceptable to argue that patients with pituitary deficiency will present with abnormal growth or puberty and thus be identified and treated. The impact of undiagnosed pituitary deficiency may be more far-reaching than this with potential consequences on other systems, including adverse effects on body composition and bone health. In addition, the effects on brain growth and neurocognitive function during a time of continuing brain development must be a concern" (p. 668).[29]

Sports-related TBI

A concussion (really just a euphemism for a mild TBI) is a well-known hazard of all contact sports. Nevertheless, there is a paucity of studies relative to the incidence of PTH and sports injuries. Kelestimur and Tanriverdi reported on the incidence of PTH in amateur kickboxing in Turkey. GH deficiency was seen in 15% and 45% of the individuals in those respective studies. ACTH deficiency was found in 0% and 9%.[30,31]

Ives reported on a 16-year-old junior soccer player who had multiple concussions 2 years prior.[32] The patient complained of fatigue and a decline in physical functioning and growth. He was found to have deficiencies of GH, thyroid, and cortisol and responded well to replacement.

Multiple concussions in collegiate and professional football in the National Football League (NFL) are common. Recurrent concussion in the NFL has been associated with development of depression, cognitive impairment, and poor quality of life in retirees.[33] Kelly et al. published on the relationship of football-related TBIs to pituitary and metabolic function in 68 retired NFL players.[34] The mean number of years in the NFL was five, and the mean number of reported concussions was three. Adjusting for the individual's BMI, they found hormonal dysfunction in 16 (23.5%) subjects. Ten subjects (14.7%) had isolated GHD; three (4.4%) had isolated hypogonadism; three (4.4%) had both GHD and hypogonadism. Metabolic syndrome was present in 50% of all the subjects, including five of six who had hypogonadism. The subjects with hormonal dysfunction trended toward lower scores in quality-of-life testing and had a higher incidence of erectile dysfunction. Although this study did not prove the direct causative link between multiple concussions and hormonal dysfunction, the index of suspicion is clearly raised. Pituitary screening should be considered in symptomatic individuals who have a history of single or multiple mild TBIs.

CLINICAL SYMPTOMS OF HYPOPITUITARISM

For those who survive a TBI, the clinical manifestations vary widely depending on the type, site, and severity of the injury, including direct or indirect injury to the hypothalamus and pituitary. Any of the hormones produced by the anterior or posterior pituitary can be affected by TBI. Release of the anterior pituitary hormones (GH, TSH, LH, FSH, and ACTH) is stimulated by the neuropeptide-releasing hormones from the hypothalamus. The posterior pituitary hormones (vasopressin, oxytocin) are produced by the hypothalamus and are carried by long axonal projections into the posterior pituitary from which they are later released. Pituitary hormones regulate many processes that are critical for normal metabolic function and normal life expectancy. As a result, deficiency of one or more of these hormones will produce diverse symptoms and signs with consequent worsened morbidity and possibly reduced life expectancy. Failure to identify hypopituitarism could adversely affect a patient's ability to adapt physically and mentally after TBI. The patient's history and physical examination may help determine whether hypopituitarism is present. Decreased ACTH may lead to complaints of weakness or fatigue or to symptoms of hypoglycemia. Patients with decreased TSH may experience cold intolerance or fatigue. Decreased testosterone, LH, or FSH may result in sexual dysfunction, menstrual abnormalities and infertility, fatigue, sarcopenia, and metabolic dysfunction. Hypogonadism has also been associated with worse functional status and possibly with worse community reintegration following TBI.[35–38] Replacement of sex hormones improves body composition, energy levels, general well-being, and in females, reduced risk of osteoporosis. In GH deficiency, body fat increases, and lean body mass decreases. Exercise tolerance is increased, together with the patient's sense of well-being and overall quality of life.[39] The GH-IGF-1 axis plays an important role in both prefrontal executive function and memory functioning. Leon-Carrion demonstrated cognitive impairments in GH-deficient patients after TBI and suggested that treatment with GH could improve cognition.[40] High et al. reported on the effect on cognition by GH replacement for a year in a double-blind study of 12 subjects who received the active medication compared to 11 subjects receiving placebo.[41] They found improvement in the active medication cohort in information processing speed, executive functioning, verbal learning, and dominant-hand finger tapping. Moreau et al. evaluated the effects of year-long GH replacement in moderate-to-severe TBI in a double-blind, placebo-controlled study.[42] They also found a moderate improvement in memory (especially immediate memory) and information processing speed. They found no change in attention, executive functioning, or language. The individuals with the greatest improvements were the ones with the more significant deficits. Reimunde et al. studied 11 active medication subjects and eight control subjects with moderate-to-severe TBIs.[43] After only 3 months of treatment, they found improvement in the treated group in the domains of vocabulary, verbal IQ, and total IQ. The anterior pituitary deficiencies with corresponding clinical symptoms are summarized in Table 15.1. Posterior pituitary deficiencies after TBI are common in the acute phase, but they

Table 15.1 Clinical signs and symptoms of hypopituitarism

Signs and symptoms	Associated hormones
Weakness, fatigue, decreased exercise tolerance	ACTH, GH, LH, FSH, TSH
Increased body fat	GH, LH, FSH
Decreased muscle mass	GH, LH, FSH
Loss of libido, erectile dysfunction, oligo/amenorrhea, infertility	LH, FSH
Ischemic heart disease	GH
Shortened life span	GH
Weight loss, weight gain	ACTH, TSH
Cognition, psychomotor speed	GH, TSH
Attention, learning	GH, TSH
Memory	GH, TSH, LH, FSH

Abbreviations: ACTH = adrenocorticotropic hormone; FSH = follicle stimulating hormone; GH = growth hormone; LH = luteinizing hormone; TSH = thyroid stimulating hormone.

usually are not permanent and are easily detectable in acute settings by assessment of urine osmolality.

Because the clinical manifestations of these anterior pituitary hormone deficiencies may be nonspecific and are often attributed to the physical and psychological sequelae of the brain trauma itself,[1] the clinical diagnosis of hypopituitarism is challenging, and the diagnosis may be delayed for months or years. Education regarding TBI and pituitary dysfunction is an important next step for endocrinologists, neurologists, neurosurgeons, physiatrists, and rehabilitation health care providers.

GUIDELINES FOR SCREENING FOR HYPOPITUITARISM

The probability of developing hypopituitarism has been based on the severity of the TBI,[1,14] especially when associated with cranial fractures, cerebral damage, and a prolonged period of loss of consciousness (LOC) (Figure 15.2).[44] Therefore, a major distinction for consideration of who to treat is based on moderate-to-severe versus mild head injury. Moderate-to-severe TBI has been extensively studied. Despite the previous paucity of studies, mild TBI has been gaining popularity recently. Ioachimescu et al. demonstrated GH deficiency in five out of 20 (25%) veterans complaining of cognitive and psychosocial dysfunction with a history of mild TBI.[45]

The most widely used clinical classification of TBI severity is the GCS. Other factors that define clinical severity of TBI include duration of LOC, posttraumatic amnesia, and intracranial lesion(s) on imaging studies.[15,44] Kelly[14] identified GCS scores of <10, diffuse brain swelling on initial CT, and hypotensive or hypoxic insults as significant predictors of developing hypopituitarism. Ripley et al.[38] found that duration of menstrual abnormalities in women following TBI was related to severity of injury. By contrast, Lieberman[46] found no correlation between severity of head

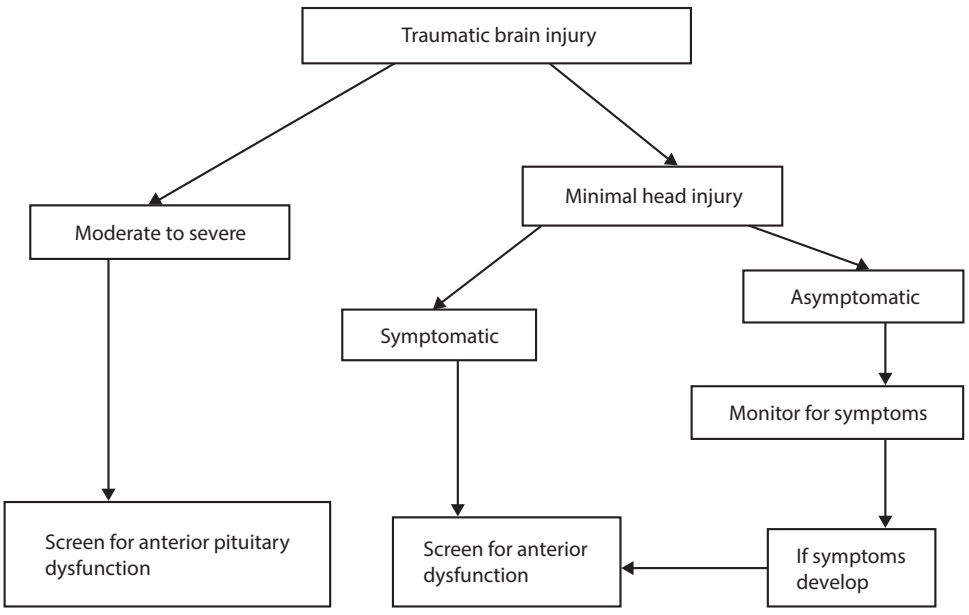

Figure 15.2 Screening for hypopituitarism based on the severity of brain injury.

injury and pituitary dysfunction as assessed by GCS.[47] Although mild TBI was not included in the study by Agha,[47] patients with severe or moderate TBI did not display a relationship between hypopituitarism and TBI severity as measured by either GCS score or CT scan findings. As well, in two prominent studies by Aimaretti, the degree of hypopituitarism was not related to the GCS or the Fisher scale (in those with subarachnoid hemorrhages).[48,49] Cranial MRI provides the most specific cross-sectional views of the hypothalamus and pituitary. Although radiographic assessment of the pituitary is often not useful in diagnosis, imaging studies may reveal the nature of the pituitary injury and help localize the insult.[50] Visualization of a pituitary stalk interruption confirms the diagnosis and is predictive of multiple anterior pituitary hormone deficiencies. However, the absence of visual damage on imaging studies does not exclude hormonal abnormalities.

Many questions remain regarding which patients are at greatest risk for TBI-induced hypopituitarism.[51,52] Techniques employed to identify and assess TBI have yielded conflicting results. Low serum IGF-1 levels are indicative of GH deficiency, but they also may be caused by other diseases or result from advancing age.[52,53] Confounding the issue even further is the lack of consensus on the criteria for defining TBI as mild, moderate, or severe.[54,55] The patients with TBI are first seen by the trauma surgeons and neurosurgeons, neurologists, and physiatrists. The rehabilitation physicians provide subsequent therapy. Because the pituitary deficiency may not be diagnosed for many years after TBI, rehabilitation physicians must continuously monitor their patient for signs and symptoms indicative of hypothalamic–pituitary impairment.

There is a body of evidence that patients with moderate-to-severe TBI need to be screened; however, physicians should also be aware of clinical symptoms of anterior or posterior pituitary dysfunction in patients with mild TBI as well. Hypopituitarism identified immediately after TBI may not always persist or require long-term treatment. Agha[47] examined the prevalence of anterior and posterior pituitary dysfunction in the acute (7–21 days) phase following TBI. This series identified deficiencies in need of immediate replacement, such as ACTH deficiency and posterior pituitary dysfunction. Aimaretti[48,49] examined head injury (TBI and SAH) in the subacute phase (3 months to 1 year). Panhypopituitarism at 3 months always showed no recovery at 1 year. Isolated hormonal deficits could change between 3 months and 1 year. In the Bondanelli study,[56] some patients developed anterior pituitary deficiencies more than 1 year after their TBI.

In conclusion, we recommend screening the moderate-to-severe TBI subject acutely for DI and ACTH deficiency. Anterior hormone screening should be considered at 3 months to make certain that a patient does not have panhypopituitarism. For most TBI patients, endocrine screening at 1 year will detect treatable deficiencies that are permanent. In TBI patients who show normal pituitary function after 1 year, the clinician should be vigilant for the development of pituitary dysfunction in the subsequent years after TBI.

ENDOCRINE TESTING

The hospital record at the time of admission should be reviewed for low GCS score and other indicators of moderate-to-severe brain injury, hypoxic and hypotensive episodes, brain swelling, and diabetes insipidus (DI), all of which may increase the probability of hypopituitarism. Although DI is routinely attributed to pituitary insult, it occurs in only ~30% of patients with both TBI and hypopituitarism, and it is usually transient. Endocrine evaluation should, therefore, be considered in spite of the absence of DI. A full endocrinologic evaluation should be considered in all patients with the aforementioned conditions. Additionally, patients with mild trauma should be considered for evaluation if they develop symptoms without the confounding physical disabilities.

For patients with TBI, pituitary gland function should be tested prospectively or retrospectively.[51] Routine basal hormonal testing should be performed for any patient hospitalized with a TBI who has symptoms such as polyuria, hyponatremia, or hypotension. Acutely, the adrenal axis should be treated. Prospectively, all patients with moderate-to-severe TBI as well as symptomatic patients with mild TBI should undergo a baseline hormonal evaluation at 3 and 12 months after the primary brain insult.

Retrospectively, all patients with any signs or symptoms of hypopituitarism with a history of moderate or severe TBI more than 12 months previously should undergo hormonal testing.

Each individual axis needs to be evaluated.[51] Basal free T4 and TSH levels should be measured to evaluate the thyroid axis. To evaluate gonadal function, baseline LH and FSH levels, together with a morning testosterone level, should be obtained in men and estradiol level, should be obtained in premenopausal women who are not menstruating regularly. Prolactin levels should be measured in all patients. A basal morning (9 a.m.) cortisol level should be measured initially to screen for severe adrenal insufficiency. If cortisol levels are <500 nmol/L (<18 μg/dL), the patient should be referred to an endocrinologist for further assessment. This involves a dynamic stimulatory test for adrenal reserve using the insulin tolerance test (ITT), glucagon stimulation test, or short ACTH (Cosyntropin) stimulation test. Patients should have normal thyroid function or be on appropriate thyroid hormone replacement before stimulation testing.

A normal serum IGF-1 level does not exclude the diagnosis of GH deficiency. Zgaljardic et al. reviewed the results of 138 individuals with moderate-to-severe TBIs who had been assessed for GHD using the glucagon stimulation test and serum IGF-1.[57] They found an IGF-1 cutoff value of 175 μg/L minimized the misclassification of GHD patients and GH-sufficient patients and provided a sensitivity of 83% and specificity of 40% as well as a negative predictive power of 90%. Hypoglycemia is the most potent stimulus

Table 15.2 Routine basal hormonal screening tests for TBI-induced hypopituitarism

Basal hormone test	Test time
Serum cortisol (morning)	9 a.m.
free T4, TSH, free T3	9 a.m.
IGF-1	9 a.m.
FSH, LH, testosterone (in men) or 17βE2 (in women)	9 a.m.
PRL	9 a.m.
Patients with polyuria: diuresis, urine density, Na++ and plasma osmolality	Any time
Dynamic testing	
Cosyntropin (ACTH) stimulation test – 250 µg ACTH i.m./i.v. and measure serum cortisol 30 and 60 minutes later (normal over 500 nmol/L or 18 µg/dL)	Any time

Source: Adapted from Ghigo, E., Masel, B., Aimaretti, G. et al., Consensus guidelines on screening for hypopituitarism following traumatic brain injury. *Brain Injury*, 19, 711–24, 2005.

Abbreviations: FSH = follicle-stimulating hormone; IGF-1 = insulin-like growth factor-1; LH = luteinizing hormone; PRL = prolactin; TSH = thyroid-stimulating hormone; UFC = urinary free cortisol.

for both somatotrophic and corticotrophic functions. The ITT is generally considered the gold standard for the diagnosis of GHD but is contraindicated in patients with a history of ischemic heart disease or epilepsy. For this reason, some clinicians prefer to avoid the ITT in TBI.[58,59] Among the classical provocative tests, a good alternative for both GH and ACTH is the glucagon stimulation test. The ITT or glucagon tests enable adrenal and GH reserve to be assessed simultaneously. Another provocative test to be considered is GHRH in combination with arginine as well with GH secretagogues.[60] One stimulation test is usually sufficient for the diagnosis of adult GHD although some funders may require a confirmatory second test. Not all patients suspected of having GHD, however, should even require a GH stimulation test for diagnosis. Patients with three or more pituitary hormone deficiencies and an IGF-1 level below the reference range most likely have panhypopituitarism and therefore should not need a GH stimulation test.

Table 15.2 outlines routine basal hormonal testing for TBI-induced hypopituitarism, and Table 15.3 provides the main provocation/dynamic tests required for diagnosis of the pituitary deficiencies.

REPLACEMENT THERAPY RATIONALE

To date, there is a paucity of data regarding the specific therapies of pituitary dysfunction secondary to the specific diagnosis of a TBI, but there is certainly no data to show that one should not use the classical criteria for the treatment of the hypopituitarism. Treatment involves replacement of individual hormones, depending on the specific deficiencies, to control signs and symptoms and to enable patients to perform normal daily activities. Once hormone dosages are determined, they generally remain unchanged except during periods of illness or other unusual stress, and there is a need for life-long treatment.[2,8] Therapy should follow the general progression of pituitary dysfunction after TBI: acute phase (1–3 weeks), subacute phase (3–12 months), and chronic (>1 year) (see Table 15.3). It is well known that pituitary hormone secretions are affected immediately after TBI, but these may not always persist or require long-term treatment. Some authors suggest that dynamic changes of pituitary hormones following acute TBI may reflect the severity of injury and also determine the outcome.[61] In the acute phase, Agha[47] demonstrated deficiencies in need of immediate replacement: ACTH deficiency (secondary adrenal insufficiency) and posterior pituitary dysfunction (DI/SIADH).

As a TBI can cause central adrenal deficiency, which can be life-threatening, hydrocortisone therapy should begin as soon as the diagnosis is confirmed by an ACTH stimulation test or other appropriate test. Acute hypocortisolemia and central DI are predictive of mortality and long-term pituitary deficits in TBI.[62] If TSH deficiency is identified, thyroid replacement therapy can start only after

Table 15.3 Summary of typical provocation tests performed by endocrinologists for hypopituitarism

Provocative agent and dosage	Assay times (minutes)	Response
Insulin-induced hypoglycemia[a] (0.05–0.15 regular insulin IU/kg i.v. at 0 min)	0, 30, 45, 60, 75, 90	Cortisol > 500 nmol/L (18 mg/dL) Normal GH: peak > 5 mg/L Severe GHD: peak GH < 3 mg/L
Glucagon stimulation test (1 mg i.m. at 0 min)	0, 90, 120, 150, 180	Cortisol > 500 nmol/L (18 mg/dL) Normal GH: peak > 5 mg/L Severe GHD: peak GH < 3 mg/L
Cosynthropin ACTH stimulation test: 250 µg i.v./i.m.	0, 30, 60	Cortisol > 500 nmol/L (18 mg/dL)
GHRH-Arginine GHRH: 1 mg/kg i.v. at 0 min; Arginine: 0.5 g/kg (max dose 30 g)	0, 30, 45, 60	Normal: peak GH > 16.5 mg/L Severe GHD: peak GH < 9 mg/L

[a] The insulin tolerance test (ITT) is considered by many as contraindicated in patients with CNS pathologies.

serum cortisol levels are normalized as thyroid hormone enhances the metabolism for cortisol and could unmask/worsen a compensated adrenal insufficiency or deficiency. Sex hormone replacement therapy may be initiated in men and in premenopausal women with LH and FSH deficiencies. Replacement of sex hormones improves body composition, energy levels, and general well-being. Replacement can also normalize sexual function and reduce the risk of osteoporosis.

There is a consensus among endocrinologists that patients with panhypopituitarism or multiple pituitary deficits should undergo immediate replacement therapy for all pituitary deficiencies with the notable exception of GHD as it is known that other pituitary hormonal deficits, once corrected, can restore the normal GH response to the provocative tests. For isolated pituitary deficit of GH, the provocative testing may be postponed until 12 months as at that point the GHD is thought to be permanent. Somewhat similar, the gonadotropic deficit is recommended to be replaced only after retesting as it is known that the gonadal function is transiently impaired as a result of concurrent stressful conditions and can recover over time. Additionally, secondary hypogonadism is not a clinical emergency.

SUMMARY

A TBI is both disease causative and disease accelerative.[63] The relationship between pituitary dysfunction and TBI is as clear as the relationship between untreated pituitary dysfunction and psychiatric, medical, and psychological morbidity. Diseases are often multifactorial in causation. As PTH clearly is one of those factors, with appropriate diagnosis and treatment, we may "cure" that cause. The need for monitoring for the development of PTH was emphatically stated in the 2009 Institute of Medicine report on the Gulf War: "That hormonal alterations substantially modify the posttraumatic clinical course and the success of therapy and rehabilitation underscores the need for the identification and appropriate timely management of hormone deficiencies to optimize patient recovery from head trauma, to improve quality of life, and to avoid the long-term adverse consequences of untreated hypopituitarism" (p. 227).[64]

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16

Neurotransmitters and pharmacology

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EDITOR'S NOTE

Pharmacological treatment of traumatic brain injury (TBI) is complex and still in its infancy as a field of clinical investigation. Patients with TBI have a wide variety of central nervous system (CNS) problems as well as numerous peripheral disorders (e.g., hypertension, reduced bowel function) that can be addressed pharmacologically. Indeed, the non-CNS medical problems in TBI patients often require the use of drugs to control hypertension or increase bowel function, and drugs that affect the autonomic nervous system are commonly used for such disorders. Two of the major difficulties in identifying useful medications for TBI patients are the diversity of brain injury encountered in this population and the complex myriad neurotransmitter systems in the brain that form the primary basis of neuropharmacology. Although this chapter focuses on the medications that are used to alter neurological or behavioral functions (i.e., those that act on the CNS), neurotransmission in the autonomic nervous system and the drugs that modify it are also described.

INTRODUCTION

Most drugs that are used for an action on the CNS, such as those employed in neurology and psychiatry, exert their action by acting at the site at which neurons communicate with one another, namely, the synapse. These drugs, therefore, exert their effect by modifying the process of "neurotransmission," a key feature of which are the "neurotransmitters." The exceptions to this rule include classes of drugs known as 1) the *local anesthetics*, which prevent nerve conduction by blocking sodium channels and, thereby, alleviating pain; 2) *general anesthetics*, which produce a reversible loss of consciousness by unknown means although recent evidence suggests these agents can also modify neurotransmission; and 3) some *antiepileptic agents*, which prevent seizures by acting directly on voltage-gated ion channels to alter nerve conduction. It should be noted that some antiepileptic drugs clearly produce their beneficial effects by altering neurotransmission (e.g., diazepam, tiagabine, perampanel).

In addition to the CNS, a large number of drugs are used to therapeutically alter neurotransmission in the peripheral nervous system (PNS), including that in the autonomic nervous system (ANS). Indeed, hundreds of PNS-acting drugs have been developed for hypertension, heart disease, gastrointestinal disorders, urinary bladder control, erectile dysfunction, hiccups, asthma, hay fever, muscular spasms, etc.

Drug classes whose mechanism of action involves a modification of central synaptic neurotransmission include narcotic analgesics (used to alleviate pain), antipsychotic agents (used to treat schizophrenia), antidepressants, antianxiety agents (e.g., diazepam or Valium®), and some antiepileptic drugs. Drugs modifying synaptic transmission in the PNS include spasmolytics and neuromuscular junction-acting agents (e.g., Botox A for facial wrinkles, tubocurarine, vecuronium, etc.).

There is some controversy concerning whether chemicals released from neurons should be referred to as *neurotransmitters* or *neuromodulators*. Some authors distinguish between neurotransmitter and neuromodulator;[1] however, we will adhere to the definition of a neurotransmitter adopted by Snyder and Ferris[2] as "a molecule released by a neuron or glia which physiologically influences the electrochemical state of adjacent cells." Thus, we only use the term *neurotransmitter* in this chapter.

The question of whether or not a substance functions as a neurotransmitter is not always an easy one to answer and requires extensive experimental testing by neuroscientists. Neurobiologists have set specific criteria that must be fulfilled before a substance is accepted as a neurotransmitter. These criteria were established in the mid-1960s by Werman,[3] and although the original criteria were extremely useful for more than 25 years, they may not be entirely adequate because knowledge of how neurons communicate with one another and with target organs in the periphery has expanded. Indeed, some of the recently discovered signaling molecules, such as the gases nitric oxide and carbon monoxide, and the endogenous lipids anandamide and 2-arachidonoyl glycerol (endocanabinoids), do not fulfill the previously established criteria yet clearly function as important neural messengers.[3–8]

Nevertheless, there are about eight small-molecule chemicals (including some amino acids) that have been well established as neurotransmitters and another 20 to 30 larger molecule substances (including peptides and steroids) that are also regarded as neurotransmitters in the nervous system. The seven well-established, small-molecule or "classical" neurotransmitters include the following:

1. Acetylcholine
2. Norepinephrine
3. Dopamine
4. 5-Hydroxytryptamine (5–HT, serotonin)
5. Gamma-aminobutyric acid (GABA)
6. Glycine
7. Glutamate/aspartate

All of these have been associated with the action of a drug or group of drugs that exert clinically useful effects (with the possible exception of glycine) on the nervous system. In addition, there are several neuropeptides that serve as neurotransmitters or neuromodulators (i.e., they modify the action of the classical neurotransmitters) and that have been associated with the action of drugs, and these are discussed. These would include compounds such as opioid peptides.

To appreciate how drugs may interact with and perhaps therapeutically modify synaptic neurotransmission in, for example, TBI, it is essential to understand the basic physiology and pharmacology of the various neurotransmitter systems in the CNS. Thus, we begin with a description of the physiology of chemical neurotransmission and then proceed to discuss the individual neurotransmitters and the drugs that mediate their effects through such neurotransmitters.

It should be kept in mind that synaptic transmission is not only important for understanding the action of drugs, but it is vital for all functions of the nervous system, and it appears to be the site at which learning and memory take place in the CNS (see chapter in this text by Lehr).

Finally, it is important to realize that any given neurotransmitter in the CNS, PNS, or both is likely a component in several distinctly separate functional systems (e.g., dopamine in the nigrostriatal system that modulates movement, dopamine in the tuberoinfundibular hypothalamic system that controls prolactin secretion, dopamine in the mesolimbic dopamine system that plays a role in reward and addiction, etc.). As such, one must be cognizant of the potential and often confounding interactions of pharmacotherapy targeting a neurotransmitter in one functional system, such as dopamine (DA) in the striatum for Parkinson's disease with "unintended" targets in the limbic and cortical DA systems. Such interactions may lead to problematic side effects.

CHEMICAL NEUROTRANSMISSION

In the mammalian nervous system (both central and peripheral), the predominant form of communication between two nerves and between nerve and muscle (or nerves and glands) is chemical. Electrical transmission between nerve cells can also occur, but it is not easily modified by drugs and is not considered here. The site at which this chemical transmission occurs is called the *synapse*. From Figure 16.1, it can be seen that the synapse consists of several cellular and subcellular structures. Although synapses can occur at several locations on a neuron that is receiving information from another neuron, the more typical arrangement is that described in Figure 16.1. Thus, the axon terminal of one neuron generally synapses on the cell body (soma or perikaryon called *axosomatic synapses*) or dendrites of another neuron (called *axodendritic synapses*). Axons may also synapse on other axons, especially at the nerve terminals (called *axo-axonic synapses*), and under unusual circumstances, dendrites may synapse with other dendrites (*dendrodendritic synapses*). Last, cell bodies may synapse with one another (*soma-somatic synapses*).

The classical neurotransmitters (listed above) are small, water-soluble, organic amines that are synthesized from precursors within the axon terminal and taken into and stored in small round or ovoid vesicles. The synaptic vesicles release their neurotransmitter from the nerve terminal in a voltage- and calcium-dependent process when an "action potential" (AP) or nerve impulse reaches the nerve terminal. Synaptic transmission involves a highly complex and cascading series of molecular events, but the basic steps associated with neurotransmitter release at a chemical synapse are as follows:

Step 1: The first step is the release of the neurotransmitter from its storage site in a vesicle upon arrival of an AP. The voltage (membrane depolarization) of the AP opens voltage-gated calcium channels that allow the influx of calcium

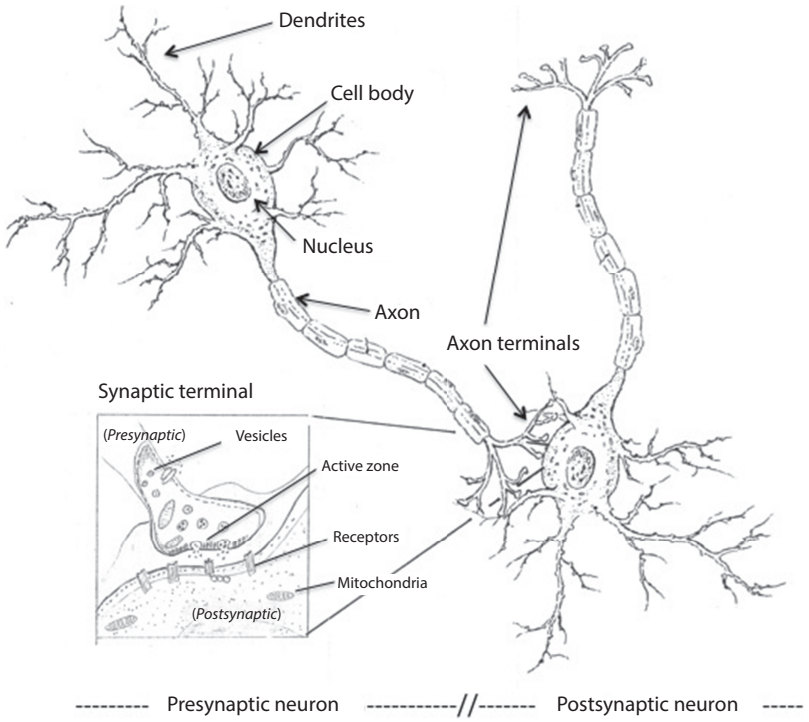

Figure 16.1 Drawing of an axosomatic (typical) synapse between two neurons. The neuron synapsing on another neuron is referred to as the *presynaptic* neuron, and the neuron receiving the input is called the *postsynaptic* neuron. Various subcellular structures associated with the synapse are labeled. Vesicles contain the neurotransmitter destined for release into the synaptic cleft. The active zone is the site at which vesicles attach to the docking sites just prior to release. (Adapted with permission from Carlson, N. R., *Physiology of Behavior*, 11th ed., Pearson Education, Inc., USA, 2013, p. 31.)

into the terminal from the extracellular fluid. The calcium then triggers a release process called *exocytosis* ("leaving the cell"). Exocytosis involves fusion of the vesicle membrane with the nerve terminal membrane and the opening of the vesicle into the synaptic cleft (Figure 16.1).[9] Fusion of the vesicle membrane with the nerve terminal membrane, leading to exocytosis of the neurotransmitter into the synaptic cleft, requires calcium that has entered the nerve terminal through channels that have been opened by the arrival of the AP. Calcium initiates the fusion process by facilitating an interaction between vesicle membrane proteins (called *V-SNARES*) with nerve terminal membrane proteins (called *T-SNARES*). The vesicle membrane then collapses into the nerve terminal membrane and extrudes its contents into the synaptic cleft. The release process may be upregulated or downregulated (i.e., facilitated or inhibited, respectively) by receptors found on the nerve terminal (called *presynaptic receptors* or *autoreceptors*). Certain pharmacological agents may have the capacity to directly interfere with neurotransmitter release or to interfere with presynaptic facilitation or inhibition. Under special circumstances, neurotransmitters can be released by a calcium-independent process that does not involve exocytosis but involves a membrane transporter. An example of the latter is the amphetamine-induced release of norepinephrine and dopamine.[10]

Step 2: The next step in synaptic transmission involves binding of the neurotransmitter to *receptors* in the postsynaptic membrane and the initiation of postsynaptic events, i.e., membrane depolarization or hyperpolarization. Receptors give both neurotransmitters and drugs their selectivity and specificity. The receptors, which are typically membrane proteins or glycoproteins, only recognize and bind chemicals of the "correct" chemical structure. Thus, just as only one key opens a lock, only a specific chemical structure can initiate postsynaptic events via its receptor (or similar receptor subtypes). The receptors for neurotransmitters come in two varieties: 1) Those that actually form an ion channel in the membrane (such as the nicotinic cholinergic receptor) and mediate rapid events when the transmitter binds are called *ligand-gated ion channels* (also referred to as *ionotropic receptors*), and 2) those that are connected to ion channels indirectly via "second messenger" molecules become activated inside the postsynaptic cell membrane when the transmitter binds to the receptor. In the latter case, the receptor is linked to a guanine nucleotide binding protein (called a *G-protein*), which functions as the link between the receptor protein and the enzyme(s) that synthesize the "second messenger." This class of receptors is referred to as *G-protein coupled receptors* (GPCR) or *metabotropic receptors*.[11]

The electrical potentials that develop in the postsynaptic cell membrane in response to receptor activation move the membrane potential either further from the threshold for triggering an AP (hyperpolarization) or move it closer to the threshold (depolarization). Hyperpolarization (inhibitory postsynaptic potentials or IPSPs) results from the opening of chloride or potassium channels in the membrane, allowing chloride to flow in or potassium to flow out. Hyperpolarization, then, inhibits postsynaptic firing of an AP in the neuron. Alternatively, depolarization (excitatory postsynaptic potentials or EPSPs) results from the opening of channels that allow both sodium and potassium to flow down their concentration gradients through the same channel. This is different from the sodium-selective channel that is involved in the propagation of the AP down the axon. If the membrane depolarization is great enough as it reaches the "trigger zone" of the axon of that neuron, the threshold for an AP will be reached, and an AP (regenerative, sodium current) will be propagated down the axon to initiate synaptic transmission from that neuron's terminals.

In the CNS, a neuron can only respond in one of two ways: 1) It either reaches threshold and fires an AP, which, in turn, propagates information to the next neuron via synaptic transmission, or 2) it is inhibited, does not fire an AP, and indeed may be highly resistant to the induction of an AP. Certain drugs have the effect of enhancing or inhibiting synaptic transmission.

Step 3: The third step in the synaptic transmission process is the postsynaptic response. An integration of excitatory and inhibitory inputs to the neuron occurs, and the stronger input (either excitatory or inhibitory) determines what the postsynaptic neuron does. If the excitation inputs reach threshold, the postsynaptic cell will be activated. Depending upon the target, an excitatory response may be the contraction of muscle, the secretion of a gland, or the activation of another neuron down the line.

Step 4: The final step in synaptic transmission consists of inactivation of the neurotransmitter in the synaptic cleft. It is essential that the neurotransmitter be removed from the synaptic cleft in order for the postsynaptic cell to repolarize and become "ready" again. This is necessary for the postsynaptic neuron to remain responsive to incoming information, such as another AP coming down the axon. The two most important mechanisms for removing the neurotransmitter from the synaptic cleft are 1) reuptake into the neuron from which it was released and 2) enzymatic degradation. Other mechanisms used to inactivate a neurotransmitter in the synaptic cleft include simple diffusion away from the cleft and uptake (transport) into other nearby cells (e.g., glial cells, muscle cells in the periphery, or other neurons). Just as the neurotransmitter can be taken up and reused by the neuron that released it, the vesicle membrane is also retrieved from the nerve terminal where it fused. Thus, vesicles are also recycled.

The fine-tuning of synaptic transmission occurs via "synaptic modulators," chemicals that are signaling molecules that do not meet the criteria of a neurotransmitter. For example, there is evidence that the release of classical neurotransmitters from axon terminals may be modified by a variety of messenger molecules synthesized and released from the postsynaptic neuron and which diffuse backward across the synapse to bind to receptors on the presynaptic axon terminal. This phenomenon is referred to as *retrograde signaling* and is the mechanism by which

the endocanabinoids (natural agonists for the marijuana receptor) and the gases (e.g., nitric oxide) function as neuromodulators.[12,13]

SITES WHERE DRUGS ACT

Drugs may either facilitate (enhance) or inhibit (reduce) neurotransmission. Some of the mechanisms by which drugs can facilitate neurotransmission include the following:

- Stimulation of the release of the neurotransmitter into the cleft.
- Increased synthesis of the neurotransmitter in the presynaptic terminal.
- Prevention of inactivation of the transmitter following release (e.g., blocking reuptake or blocking enzymes of degradation).
- Stimulation of the postsynaptic receptors directly to produce a response. A drug that does this is called an *agonist*.

Some of the mechanisms by which drugs inhibit neurotransmission include the following:

- Inhibition of the synthesis of the transmitter
- Prevention of transmitter release
- Interference with neurotransmitter storage in the vesicle
- Blocking the neurotransmitter receptor or functioning
- Acting as an inverse agonist at the receptor

A drug that binds to a receptor, blocking the neurotransmitter action but producing no effect, is called an *antagonist*. A drug that binds to a receptor and produces an effect opposite that of the agonist is called an *inverse agonist*. Because of the discovery of inverse agonists, the term *neutral antagonist* is sometimes used to describe a drug that binds to the receptor and produces no effect.[14] Inverse agonists are drugs that bind to GPCRs that have constitutive activity (i.e., a GPCR that is spontaneously active in the absence of any agonist or ligand). The inverse agonist binds to the GPCR and blocks the constitutive activity.[15]

In the sections that follow, we consider the individual neurotransmitters and the drugs that produce clinical effects by altering chemical neurotransmission.

ACETYLCHOLINE (ACh)

ACh is one of the most widely studied neurotransmitters and one of the oldest, phylogenetically. It was, in fact, the neurotransmitter for which chemical neurotransmission was originally demonstrated when it was found to be released from nerves innervating the frog heart by Loewi in 1921.[16] It has been most thoroughly studied in the PNS, where it functions as a neurotransmitter of the motor neurons innervating skeletal muscle (involved in the voluntary control of movement). ACh is also the neurotransmitter of the preganglionic sympathetic and parasympathetic fibers as well as the postganglionic parasympathetic fibers.[16,17] The response to stimulating parasympathetic nerves innervating various organs in the body is shown in Table 16.1. As you can see, these nerves affect every organ in the body. Drugs that alter neurotransmission at these synapses can have very profound effects.

ACh is also a neurotransmitter in the CNS, where specific pathways have been identified in the brains of primates and other species. Basically, there are two groups of ACh neurons (cell bodies) from which axonal pathways project:[17] 1) those pathways innervating the forebrain (cell bodies in the basal forebrain in and around the medial septum and nucleus basalis of Meynert) as well as the interneurons in the striatum (basal ganglia) and 2) those innervating the brain stem and diencephalon (cell bodies in the laterodorsal tegmental nucleus and the pedunculopontine tegmental nucleus). Some of the proposed functions of ACh in these CNS pathways are given in Table 16.2, but clearly, there is much to learn about the intricate details of how ACh regulates such things as learning and memory, sleep, seizures, and emotional states, each of which are or may be changed following TBI (see below). First, however, it is essential to review the physiology and pharmacology of ACh.[1]

Synthesis, storage, release, and inactivation of ACh

Neurons that utilize ACh as a neurotransmitter are referred to as *cholinergic* neurons, and a schematic diagram of such a neuron is shown in Figure 16.2. ACh is synthesized within cholinergic neurons from the precursors, *choline* and *acetyl CoA*. Choline that comes from the diet and phospholipids, derived from the liver, circulate in plasma.[18] Some of the choline that is taken up into cholinergic neurons for synthesis of ACh comes from the enzymatic degradation of released ACh (Figure 16.2). In fact, about 50% of the choline released as ACh is recaptured by the neuron for the synthesis of more ACh.[1]

Choline is transported into the nerve by a transporter or "carrier" protein in the membrane. The choline transporter, referred to as *ChT*,[19] has a high affinity for choline, which means that it avidly picks up choline from the surrounding area. It has, however, a limited number of transport sites, meaning that it can get filled up or saturated. Increasing the concentration of choline up to the point at which the sites become filled results in a proportional increase in the rate of choline transport. However, once all the transporters are occupied, the rate of transport becomes constant.

Theoretically, one should be able to increase the synthesis of ACh by increasing the availability of choline, especially because the enzyme that converts choline to ACh, choline acetyltransferase (ChAT), is not saturated with substrate (choline).

The other precursor in the synthesis of ACh is called *acetylcoenzyme A* (acetylCoA). AcetylCoA derives from pyruvate via the breakdown of glucose and is, therefore, plentiful inside the neuron and is not a limiting factor in the synthesis of ACh.

Table 16.1 Organ response to parasympathetic nerve stimulation

Organ receiving innervation	Response to stimulation	Receptor type
Eye		
Iris, sphincter	Pupillary constriction (miosis)	Muscarinic
Ciliary muscle	Contraction—near vision	Muscarinic
Heart		
SA node	Decrease in heart rate	Muscarinic
Atrium	Shortens refractory period	Muscarinic
AV node	Slows conduction	Muscarinic
Ventricles	No response—poor innervation	
Vasculature	No parasympathetic innervation (has muscarinic receptors that can respond with vasodilation)	Muscarinic
Trachea and bronchioles	Constriction	Muscarinic
Stomach and intestine	Increase in motility, tone, and secretions; relaxation of sphincters	Muscarinic
Urinary Bladder		
Detrusor muscle	Contraction, bladder emptying	Muscarinic
Trigone and sphincter	Relaxation	Muscarinic
Sex organs, male	Erection	Muscarinic
Sweat glands	Secretion	Muscarinic
Lacrimal glands	Secretion	Muscarinic
Nasopharyngeal glands	Secretion	Muscarinic

Source: Westfall, T. C. and Westfall, D. P. Neurotransmission: The autonomic and somatic motor nervous systems, in Brunton, L. L., Chabner, B. A., and Knollmann, B. C., Eds., *The Pharmacological Basis of Therapeutics*, 12th ed., McGraw-Hill Medical Publishing, New York, 2011, 111.

Table 16.2 Some proposed functions of ACh in the CNS

Learning and memory (cholinergic neurons lost in Alzheimer's disease)
Sleep and arousal states
Body temperatures
Susceptibility to seizures
Affective states (mood)
Cardiovascular function via hypothalamus
Motor disorders (Parkinson's disease)
Psychosis (schizophrenia)

Experimental studies have established that the rate-limiting factor in the overall synthesis of ACh is the uptake of choline by the neuron.[1,20] Because ACh neurons are lost in Alzheimer's disease, it has been of interest to attempt to increase ACh synthesis in the brains of Alzheimer's patients. Although some studies have suggested that this is possible, choline has not been found terribly useful for improving memory in this or other populations.[21] The reason for this may be twofold: 1) Many of the cholinergic neurons (in the basal forebrain) that would otherwise synthesize ACh (in their terminals) have died, and 2) the choline transporters of the few remaining cholinergic neurons would be readily saturated with choline, thus limiting the overall synthesis and availability of ACh as a neurotransmitter in the brain. An additional problem is that choline in the plasma may not be readily available to the neurons in the brain because it has difficulty crossing the blood–brain barrier.[19] There are no known drugs to increase the uptake of choline although there are experimental drugs that inhibit the uptake of choline and thus interfere with the synthesis of ACh. Hemicholinium-3 and triethylcholine are both competitive inhibitors of choline uptake (thus inhibiting cholinergic neurotransmission). Experimental compounds such as these, if approved for use in humans (which they are not), would certainly be contraindicated in persons with diseases such as Alzheimer's disease.

Choline can also get into neurons by another mechanism, called *"low-affinity" uptake*, which may account for the increase in synthesis of ACh that is seen in some peripheral organs following the administration of high doses of choline. Much higher concentrations of choline are required to saturate the transport proteins involved in low-affinity transport.

It has been hypothesized that the selective vulnerability of cholinergic neurons in Alzheimer's disease may be due to the double role of choline in forming membrane phospholipids and ACh in these neurons. Especially in choline

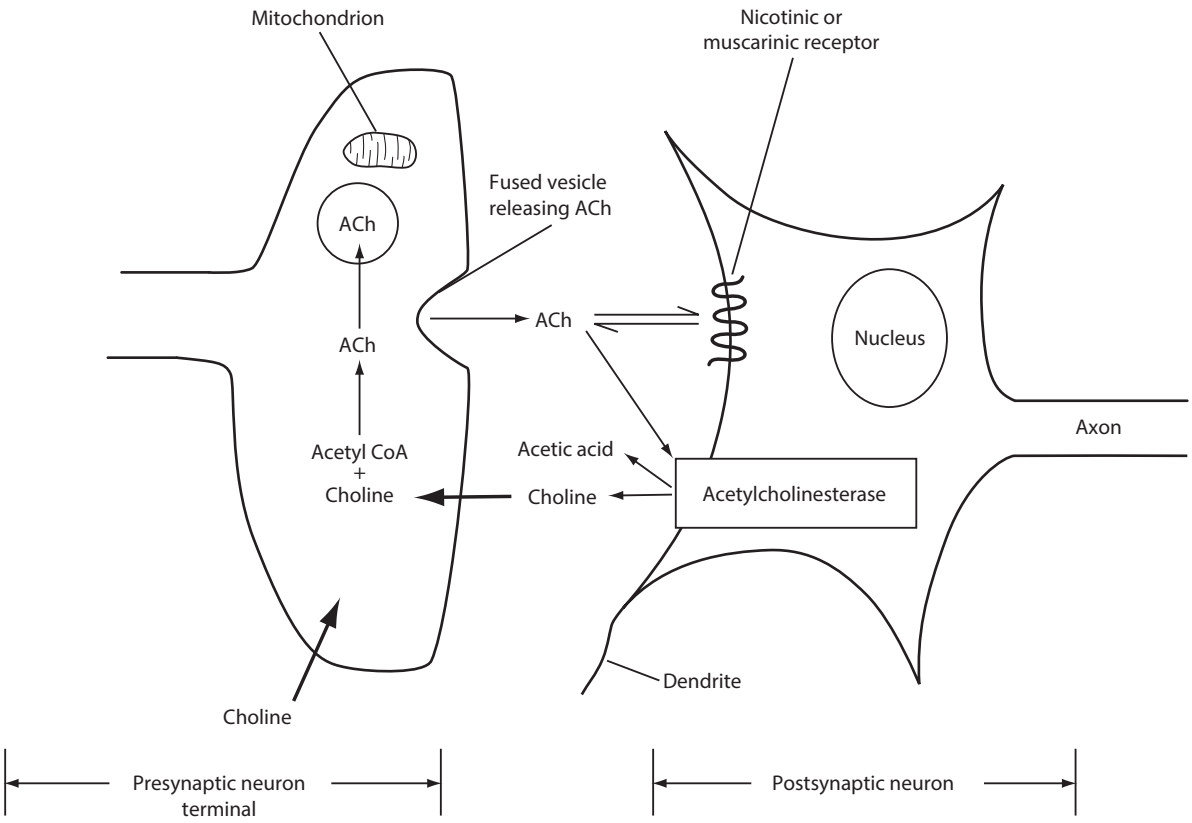

Figure 16.2 Drawing of a cholinergic synapse showing the fate of ACh after release into the synaptic cleft. Note that the neuron utilizes choline from two sources: 1) the blood and 2) that which is recycled from the breakdown of released ACh in the synaptic cleft. Acetylcholinesterase associated with the postsynaptic membrane terminates the action of released ACh.

deficiency, the breakdown of cell membranes to shunt choline into the neurotransmitter synthesis pathway may lead to membrane damage and cell death.[22] If the latter hypothesis is true, treatment with choline may be beneficial. There is evidence that giving choline to rats can increase the release of ACh in the striatum,[23] and this effect can apparently be enhanced by caffeine.[24]

The enzyme that catalyzes the synthesis of ACh is ChAT, which is found both as a soluble enzyme (nonmembrane bound) in the cytoplasm and as a particulate enzyme (membrane bound) in cholinergic neurons.[1] Most experts believe the soluble form of the enzyme is responsible for the majority of ACh being released from the neuron. The gene responsible for forming ChAT is expressed only in cholinergic neurons, and this enzyme, therefore, serves as a phenotypic marker for cholinergic neurons. The overall synthetic scheme is given in Figure 16.3.

Once ACh is synthesized, it is stored in small spherical (synaptic) vesicles along with several other constituents, including adenosine triphosphate (ATP) and a protein called *vesiculin*. The sequestration of the ACh within synaptic vesicles serves to protect it from destruction by the

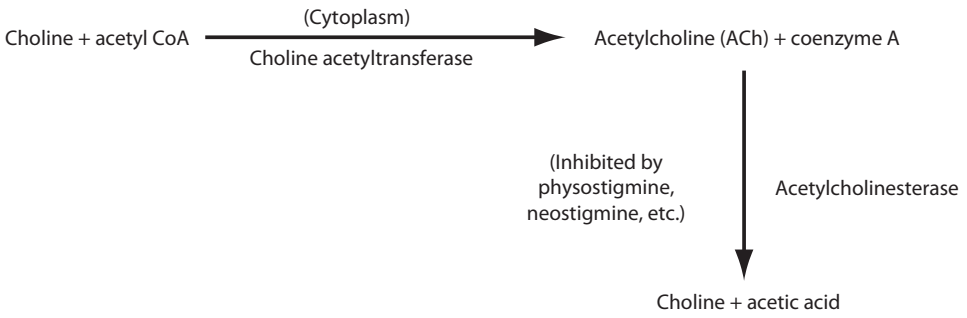

Figure 16.3 Synthesis and enzymatic degradation of acetylcholine (ACh). ACh is synthesized in the cytoplasm of the nerve terminal where choline acetyltransferase (synthetic enzyme) is found. Acetylcholinesterase (degradative enzyme) is associated with the postsynaptic membrane.

enzyme acetylcholinesterase and is essential for neurotransmitter release. Uptake into synaptic vesicles is accomplished by the vesicular ACh transporter (VAChT) that uses an electrochemical gradient produced by a proton pump-type ATPase. The VAChT transports ACh from the cytosol into the vesicle by exchanging two hydrogen ions (protons) for one molecule of ACh.[25] Although there appears to be some ACh in the cytoplasm of the neuron, the vast majority is found within the vesicles from which it is released directly into the synaptic cleft as previously described.

To reiterate, exocytosis requires that the vesicle membrane fuse with the neuron membrane and "empty" its contents into the cleft in an all-or-none process. Some of the ACh that is free within the cytoplasm of the neuron may have just been synthesized and was en route to being taken up by the vesicle membrane transporter[1] (VAChT) for storage within the vesicle. Certain compounds can interfere with this process and thus the storage of ACh in the terminals. The only drug currently known to interfere with the storage of ACh is *vesamicol*, which blocks the uptake of ACh into the vesicle and prevents the release of newly synthesized ACh.[19,26]

Considerable electrophysiological and morphological evidence also indicate that ACh is released from neurons by exocytosis.[1,19] Some toxins are known to inhibit ACh release, including botulinum toxin A and B.[16] Botulinum toxin A (*onabotulinumtoxinA*, Botox®) is commercially available and can be injected directly into muscles to block ACh release and relax the muscle. Botulinum toxin A is approved for the treatment of blepharospasm, cervical dystonia, urinary incontinence, migraine headache, and facial wrinkles.[27]

Once ACh has been released from the neuron, it can diffuse to the postsynaptic receptor (see the following section for ACh receptor subtypes) to mediate a response in the postsynaptic neuron. However, it must then be inactivated if the synapse is to remain functional. In the case of ACh, inactivation occurs by *enzymatic destruction* of the neurotransmitter. Almost all other neurotransmitters (except for the peptides) are inactivated by reuptake into a neuron. Thus, ACh is unique among neurotransmitters in terms of the mechanism of inactivation following release into the synaptic cleft.

The enzyme that degrades ACh is called *acetylcholinesterase*. However, several cholinesterases have been found in the body. One of them circulates in plasma and is known as *pseudocholinesterase* or *butyrylcholinesterase*, which hydrolyzes butyrylcholine faster than ACh.[1] Acetylcholinesterase is associated with the synaptic cleft where it is attached to both the presynaptic and postsynaptic membranes.[19] This enzyme has been shown to exist in several molecular forms that differ in their lipid solubility and in the way they attach to membranes. Several inhibitors of acetylcholinesterase are available, and these produce a dramatic increase in the concentration of ACh in the body. Such drugs are widely used in medicine and are discussed in the following.

Acetylcholine receptors

Like other neurotransmitters, ACh produces its effects and obtains its selectivity by binding to specific receptors in the postsynaptic cell membrane. These receptors chemically recognize ACh and allow it to interact with specific functional groups in the receptor. Based on the early studies of Dale,[28] which were confirmed and extended by modern biochemical techniques, it is now known that there are two major types of ACh receptors, both of which were first identified in the PNS: 1) ACh receptors at which nicotine can mimic the action of ACh are called *nicotinic receptors*, and 2) ACh receptors that are activated by the alkaloid muscarine (from mushrooms) are called *muscarinic* receptors. In the PNS, the nicotinic receptors are found at the 1) neuromuscular junction (voluntary nerves to skeletal muscle), 2) the autonomic ganglia, and 3) the adrenal medulla, and muscarinic receptors are found at the effector organs innervated by the postganglionic parasympathetic fibers (e.g., heart, gastrointestinal [GI] tract, exocrine glands). Both types of ACh receptors have been found in the brain.

NICOTINIC RECEPTORS

Nicotinic acetylcholine receptors (nAChR) have been widely studied, and most of our knowledge about nicotinic receptors comes from work on electric fish, such as the Torpedo, which uses its electric organs to kill prey. It turns out that the high voltage in these fish is generated by ACh receptors, which are highly concentrated in the electric organ. Thus, the electric fish has served as a rich source of nicotinic receptor protein for biochemists to study.

The nicotinic receptor was found to be a ligand-gated ion channel composed of five subunits with two *alpha*, and one each of a *beta*, *gamma*, *delta*, or *epsilon* subunit.[29] The ACh binds to the alpha subunit of the receptor, and because there are two alpha subunits in each receptor, it takes two molecules of ACh to open the ion channel. The techniques of molecular biology (genetic engineering) have contributed greatly to our knowledge of the nicotinic receptor as well as to our knowledge of the molecular structure of other receptors. These studies have led to a widely accepted model of the nicotinic receptor at the neuromuscular junction of mammals.

However, the nAChR associated with neurons (e.g., the autonomic ganglia and in the brain) appear to be slightly different from the skeletal muscle nicotinic receptor (i.e., neuromuscular junction). For example, it has long been known that neuronal nicotinic receptors are not blocked by the classical neuromuscular nicotinic antagonist *d*-tubocurarine but are blocked by hexamethonium, another nicotinic antagonist. These differences could be attributed to different receptor subunit composition. Indeed, some nAChRs found in the brain are homomeric, meaning that they are composed of five identical subunits (e.g., the alpha-7 nAChR). Research on neuronal nicotinic receptors is still quite active and has important bearing on nicotine addiction and Alzheimer's disease because

nicotine has been shown to increase the release of ACh in the cerebral cortex.[30,31] There is also some evidence that nicotinic receptor agonists may be beneficial in memory recall that is impaired in Alzheimer's disease. Nicotine may also stimulate nAChRs in the hippocampus to have beneficial effects in schizophrenia.[32] A mutant form of the nAChR has been implicated in one heritable form of epilepsy.[33] Neuronal-type nicotinic receptors have also been identified in non-neural cells (e.g., glial cells, endothelial cells, cancer cells), and there is evidence that some of these may play a role in promoting cancer in smokers.[34]

MUSCARINIC RECEPTORS

Muscarinic receptors are thought to make up the majority of the ACh receptors in the mammalian brain. Unlike nicotinic receptors, the muscarinic receptors are linked to G-proteins and second messengers that carry the signal to ultimately produce a response or change in the cell. Based on molecular cloning technology, five subtypes of muscarinic receptor have been identified.[19,35] The basic chemical structure (i.e., the amino acid sequence) of these muscarinic receptors has been determined. The best described of the muscarinic receptors are the so-called M1, M2, and M3, which correspond to the m1, m2, and m3 cloned receptors.[19] The muscarinic receptors are G-protein linked, mediate their effects through second messengers, and may cause either excitation or inhibition in the brain. These effects are usually produced by the opening (inhibition) or closing (excitation) of K^+ channels (i.e., potassium channels).

All GPCRs consist of a polypeptide chain (protein) with seven hydrophobic regions (i.e., areas containing amino acids that are more lipid than water-soluble).[11,19] It has been found that these hydrophobic regions of the molecule correspond to positions at which the protein loops (crosses) through the cell membrane. So these receptors loop back and forth through the membrane seven times and are said to contain *seven membrane-spanning regions*. Other GPCRs with seven membrane-spanning regions include the adrenergic, dopaminergic, and serotonergic receptors (see the following text).

The M1, M3, and cloned m5 subtypes are excitatory and increase phospholipase C activity in the postsynaptic cell via a G-protein called G_q.[11] The activation of phospholipase C by these muscarinic receptors and G_q leads to the hydrolysis of phosphatidyl inositol and the formation of diacylglycerol (DAG) and inositol triphosphate (IP_3). These molecules, in turn, function as second messengers to further activate protein kinase C and increase intracellular calcium levels, respectively.

The M2 and M4 receptors result in the inhibition of adenylate cyclase by acting through a G_i protein and, in addition, may activate (open) K^+ channels directly. These effects mediated by the M2 receptor provide the mechanism by which ACh slows the heart rate as shown in Table 16.1.[36]

Atropine is a nonselective antagonist for all muscarinic receptors, *pirenzepine* is selective for the M1 receptor, and *AFDX 116* and *methoctramine* are antagonists for the M2 receptor. The release of ACh and other neurotransmitters may be partially regulated by the activation of M2 receptors located on presynaptic nerve terminals.[37]

Clinically useful drugs that alter cholinergic neurotransmission

FACILITATORS OF CHOLINERGIC NEUROTRANSMISSION

Cholinergic agonists

There are a number of cholinergic agonists (drugs that bind to the receptor and produce a response or mimic the action of ACh), but only the muscarinic agonists find significant clinical usefulness. These drugs are primarily used in ophthalmology to treat glaucoma or to treat bowel and bladder retention postoperatively.

Muscarinic agonists include *acetylcholine*, which is not used systemically because it is rapidly destroyed by acetylcholinesterase or butyrylcholinesterase but is available for intraocular use (Miochol-E®); *methacholine* (Provocholine®), which is only partially sensitive to the action of acetylcholinesterase and is available as a diagnostic tool; *bethanechol* (Urecholine®), which is used for bowel and bladder hypofunction; *carbachol* (Isopto-Carbochol®), which is used to treat glaucoma and has some nicotinic agonist activity as well; and *pilocarpine*, a naturally occurring alkaloid found in plants, which is a potent muscarinic agonist used to treat glaucoma. Pilocarpine is given in eye drops applied topically to the eye or systemically for the treatment of xerostomia (Salagen®).

All of these drugs are used for their effect on the peripheral ANS rather than the CNS. Presumably, some of these agonists have some difficulty crossing the blood–brain barrier. However, when given in high doses, pilocarpine gets into the brain and causes seizures in experimental animals.[38] Another muscarinic agonist, *oxotremorine*, seems to produce marked effects on the brain at low doses in that it produces many of the symptoms of Parkinson's disease. Based on the apparent role of the ascending cholinergic neurons in the brain in regulating states of consciousness, it seems possible that cholinergic agonists that enter the brain produce arousal and insomnia. Indeed, even small doses of pilocarpine, given intravenously in cats, have been shown to produce arousal.[36] Arecoline is a muscarinic agonist, occurring in betel nuts, which are sometimes chewed in Asian or Indian cultures to produce CNS arousal.[39] *Cevimeline* (Evoxac®), an M1 and M3 agonist, is now used to treat xerostomia (dry mouth) of Sjogren's syndrome.[11]

There are two therapeutically useful nicotinic agonists for the treatment of tobacco dependence: nicotine itself, which is available in patches or gum to treat smokers' dependence, and *varenicline* (Chantix®), which binds to the alpha4/beta2 nicotinic receptor and relieves the cravings and withdrawal symptoms.[40] Given the fact that the neuronal nicotinic receptor is damaged by beta amyloid in Alzheimer's disease,

it is likely that we will soon see some new nicotinic drugs that are useful in treating this disorder.[41]

Cholinesterase inhibitors

Other than agonists, the only drugs used clinically to facilitate cholinergic neurotransmission are the inhibitors of acetylcholinesterase. These include the reversible cholinesterase inhibitors, such as *physostigmine* (Antilirium®), *neostigmine* (Prostigmin®), *pyridostigmine* (Mestinon®), and *edrophonium* (Tensilon®), that are used to treat or diagnose myasthenia gravis. Physostigmine crosses the blood–brain barrier, and others do not due to their highly charged molecular structure. ***Tacrine*** (Cognex®), *donepezil* (Aricept®), *rivastigmine* (Exelon®), and *galantamine* (Razadyne®) are also lipid-soluble reversible cholinesterase inhibitors that easily reach the brain. These drugs are approved for the treatment of memory and cognitive impairment associated with Alzheimer's disease. Additionally, there are several irreversible inhibitors of cholinesterase, such as the *organophosphates* (e.g., diisopropylfluorophosphate or DFP), which irreversibly inhibit the enzyme and are used primarily as insecticides. However, some of these are present in eye drops for the treatment of glaucoma. Obviously, the irreversible cholinesterase inhibitors are extremely toxic and are of interest because of their toxicological effects. They are too dangerous for systemic use.

INHIBITORS OF CHOLINERGIC NEUROTRANSMISSION

Muscarinic antagonists

Alkaloids present in the belladonna plant have long been used as muscarinic antagonists. These include *atropine* and *scopolamine* (hyoscine), both of which are nonselective muscarinic antagonists and which readily enter the brain after systemic administration. Some antimuscarinic agents, such as *benztropine* (Cogentin®), are used exclusively for their effect on the brain. The latter compound has been used to prevent the Parkinsonian-like side effects associated with antipsychotic drugs such as Haldol®. In the days before H_2 histamine receptor antagonists (e.g., cimetidine) and proton pump inhibitors (e.g., omeprazole), which are among the most commonly used ulcer drugs, atropine and other belladonna alkaloids were used to treat gastric ulcers and other conditions associated with increased GI activity. However, *pirenzepine*, the M1 selective antagonist, has been found to be better at reducing gastric secretion. Newer muscarinic antagonists *ipratropium* (Atrovent®) and *tiotropium* (Spiriva^x) are delivered in an aerosol in the treatment of bronchial asthma. Anticholinergic drugs reduce bronchial secretions and cause bronchodilatation, while decreasing GI activity and dilating the pupils. Hence, they are also used by ophthalmologists to dilate the pupils for examination of the retina. When there is hypersecretion of saliva or bronchiolar secretions, as there is during general anesthesia, atropine or other antimuscarinic drugs (e.g., glycopyrrolate) are also used to reduce secretions and to dilate bronchiolar passages.

Nicotinic antagonists

Nicotinic antagonists, at the present time, may be divided into two general categories: 1) those that are muscle nicotinic receptor antagonists or so-called *neuromuscular blockers*, such as *d-tubocurarine* (curare, the South American arrow poison), and 2) the neuronal nicotinic antagonists or so-called *ganglionic blockers*, such as *hexamethonium*, *mecamylamine* (Inversine®), and *trimethaphan*. The only ganglionic blocker still available in the United States is mecamylamine. Neuromuscular and ganglionic blockers interfere with neurotransmission by acting on the postsynaptic nicotinic receptor (an ion channel) and binding to it in a competitive or noncompetitive manner to prevent the binding of ACh to the receptor. The drugs that act at the neuromuscular junction to produce muscle paralysis bind directly to the nicotinic receptor, preventing access of ACh. This is also how some of the ganglionic blocking agents work (e.g., mecamylamine, trimethaphan). However, some of the ganglionic blockers (e.g., hexamethonium) enter the ion channel and form a plug, which also effectively interferes with neurotransmission by preventing influx of sodium ions.[42]

The neuromuscular blocking agents are also classified into two types: 1) depolarizing blockers and 2) nondepolarizing blockers. *Succinylcholine* (Anectine®) is the only clinically useful and best-known depolarizing blocker available. It binds to the nicotinic receptor at the neuromuscular junction and produces a depolarization of the membrane, which remains in persistent depolarization for a long time, rendering the synapse nonfunctional. After a period of time, the neuromuscular block actually converts to a competitive-type block, which is called *Phase II*. Giving a cholinesterase inhibitor will not antagonize the action of a depolarizing blocker and, in fact, may make the block worse. On the other hand, nondepolarizing blockers such as *d*-tubocurarine, *atracurium*, *vecuronium* (Norcuron®), and *pancuronium* (Pavulon®) are competitive neuromuscular blockers that compete with ACh for the receptor. Thus, administering a cholinesterase inhibitor (e.g., physostigmine or neostigmine) can reverse the block produced by competitive antagonists, such as *d*-tubocurarine. All neuromuscular blockers and most ganglionic blockers have a charged nitrogen atom and, therefore, do not get into the brain when injected systemically. In fact, if they are injected into the cerebrospinal fluid, they typically cause seizures. Mecamylamine, on the other hand, is a ganglionic blocking agent and a secondary amine that can enter the brain. Ganglionic blockers are used to lower blood pressure during removal of tumors of the adrenal gland, and neuromuscular blockers are used to relax (or paralyze) muscles during endoscopic examinations, surgery, and electroconvulsive shock therapy.

Cholinergic drugs in the TBI patient

There is evidence of changes in ACh neurotransmission following TBI. Immediately following injury, there appears to

be a hyperfunction of the cholinergic system, which lasts 15 minutes to 4 hours. During this time, administration of antimuscarinic drugs has been shown in animal studies to enhance the recovery of function.[43] This is followed by a period of cholinergic hypofunction in which administration of cholinergic agonists can ameliorate cognitive deficits. Thus, timely administration of cholinesterase inhibitors, such as those used in Alzheimer's disease (e.g., tacrine, donepezil, rivastigmine, or galantamine), may be beneficial for improving memory in TBI patients. Indeed, donepezil was found to improve memory in two TBI patients.[44]

Experimental evidence of cholinergic involvement in TBI is intriguing. First, there is evidence that cholinergic neurons in the brain are vulnerable to TBI and that evoked release of ACh following TBI is compromised.[45] Second, it has been found that TBI causes a loss of alpha-7 nAChRs in the brain and that treatment with dietary choline in rats subjected to TBI can restore the nAChRs and protect against memory loss as well as reduce inflammation and cell loss.[46] The primary role of ACh acting through nAChRs in the brain appears to be presynaptic modulation of the release of other neurotransmitters, including DA, NE, 5-HT, Glu, and GABA,[1,19,47] each of which have been implicated in one way or another in TBI-related dysfunction (memory loss, anxiety, etc.). Thus, the reduced release capacity of ACh itself coupled with loss of nAChRs in the brain following TBI[48] could dramatically alter CNS function through loss of presynaptic regulation of a wide variety of neurotransmitter systems. Moreover, as cited by Posadas and coworkers,[49] nicotine appears to be protective against both necrotic and apoptotic processes, (both of which occur in TBI). Parenthetically, there is considerable epidemiological evidence of an inverse relationship between smoking (presumably due to nicotine and nAChRs) and the incidence of Parkinson's disease (neurodegeneration). Last, there is evidence that supports an increased risk of Alzheimer-type neurodegeneration following, especially, repeated TBI.[50–52] Additionally, repeated TBI is now known to precipitate, even in young individuals, a condition referred to as chronic traumatic encephalopathy, which appears to be correlated to behavioral instability and decline.[53,54] Thus, continued examination and research regarding the cholinergic neurotransmitter systems and perhaps dietary choline supplementation in the context of TBI and neuroprotection seems warranted. Indeed, various forms of choline, such as cytidine-5′-diphosphate choline (CDP-choline), have shown to improve cognitive deficits following TBI in rats.[55]

NOREPINEPHRINE

Norepinephrine (NE) is one of three endogenous chemicals known as *catecholamines* that function as neurotransmitters in the mammalian nervous system. Neurons that synthesize and use NE as a neurotransmitter are often called "noradrenergic," owing to the term noradrenaline (the European term for norepinephrine). The other two catecholamines are epinephrine (Epi or adrenaline), which is a neurotransmitter in the brain but a hormone in the periphery, and dopamine (DA), which is a neurotransmitter in the brain. NE is also the neurotransmitter of the sympathetic postganglionic fibers of the ANS, in which it is involved in such things as increasing heart rate, constricting blood vessels or raising blood pressure, reducing gastrointestinal motility, and dilating pupils (see Table 16.3 for the response of various organs to sympathetic nerve stimulation). There are some exceptions to the rule that all postganglionic sympathetic nerves are "noradrenergic" (i.e., use NE as a transmitter), namely, those postganglionic sympathetic fibers going to eccrine sweat glands and those going to certain blood vessels in lower mammals. These both use ACh as a transmitter.

The finding that catecholamines form fluorescent compounds in tissue exposed to formaldehyde gas greatly facilitated the mapping of such neurons in the brain. The technique known as *fluorescence histochemistry* was developed by Falk and Hillarp in Sweden in the early 1960s.[56]

Noradrenergic neurons in the brain are found in one of two systems: 1) the locus coeruleus system and 2) the lateral tegmental system. A description of these two systems is beyond the scope of this chapter but can be found in an excellent review by Moore and Bloom.[57] Histochemical studies showed that the NE axons from the cell bodies of these two regions have a very widespread distribution in the brain, reaching essentially all levels of the neuraxis. For example, a relatively small number of NE neurons in the nucleus locus coeruleus within the pons innervate everything from the cerebral cortex to the spinal cord. The diffuse nature of NE innervation in the brain allows this system to have global influences on brain function. The NE system in the brain has been implicated in a wide variety of functions,[58] including anxiety, affective states (mood), arousal, cognition, learning and memory, REM sleep, aggression, pain perception, pleasure experience, appetite regulation, seizures, and endocrine function, all of which are or may be changed by TBI (discussed in the following). First however, we review the physiology and pharmacology of NE.

Synthesis, storage, release, and inactivation of NE

NE is synthesized in CNS neurons and PNS postganglionic sympathetic neurons from tyrosine, a dietary amino acid that can also be formed from phenylalanine in the liver. Phenylalanine is referred to as an essential amino acid because it must be supplied in the diet. Tyrosine is transported into noradrenergic neurons by a high-affinity uptake transporter.[59] Once inside the neuron, tyrosine is converted to NE by the reactions shown in Figure 16.4.

The "rate-limiting" enzyme in the overall synthesis of catecholamines (NE, DA, and Epi) is tyrosine hydroxylase, which is found in the cytoplasm of the neuron. This enzyme utilizes molecular oxygen and tyrosine as substrates and requires iron and tetrahydrobiopterin as cofactors. Under most conditions, the concentration of tyrosine in the

Table 16.3 Organ response to sympathetic nerve stimulation

Organ receiving innervation	Response to stimulation	Receptor type
Eye		
Iris, radial muscle	Dilation (mydriasis)	$Alpha_1$
Iris, ciliary muscle	Relaxation of far vision	$Beta_2$
Heart		
SA node	Increase in heart rate	$Beta_1$
Atrium	Increase in contractility	$Beta_1$
AV node	Increased conduction velocity	$Beta_1$
Ventricle	Increased contractility	$Beta_1$
Vasculature		
Skin and mucosa	Constriction	$Alpha_1$
Skeletal muscle	Constriction, dilation	$Alpha_1$, $Beta_2$
Cerebral	Constriction	$Alpha_1$
Abdominal viscera	Mostly constriction, some dilation	$Alpha_1$, $Beta_2$ for dilation
Trachea and bronchioles	Relaxation	$Beta_2$
Stomach and intestine	Decrease in motility and tone and secretion; contraction of sphincters	$Alpha_1$, $Alpha_2$ $Beta_2$
Urinary Bladder		
Detrusor muscle	Relaxation	$Beta_3$
Trigone and sphincter	Contraction	$Alpha_1$
Sex organ, male	Ejaculation	$Alpha_1$
Sweat glands	Localized secretion (palms of hands)	$Alpha_1$
Lacrimal glands	Slight secretion	$Alpha^1$
Nasopharyngeal glands	No direct innervation	–

Source: Westfall, T. C. and Westfall, D. P. Neurotransmission: The autonomic and somatic motor nervous systems, in Brunton, L. L., Chabner, B. A., and Knollmann, B. C., Eds., *The Pharmacological Basis of Therapeutics*, 12th ed., McGraw-Hill Medical Publishing, New York, 2011, 111.

neuron saturates the enzyme, so excess tyrosine or phenylalanine in the diet, for example, would not lead to increased levels of the catecholamines.[60] However, under conditions of increased utilization (e.g., stress), it may be possible to increase the rate of NE synthesis by administering tyrosine,[60, 61] especially if coupled with a dietary deficiency.

The second step in the pathway, the conversion of dihydroxyphenylalanine (DOPA) to dopamine, requires aromatic-L-amino acid decarboxylase, which uses pyridoxal phosphate (vitamin B_6) as a cofactor (Figure 16.4).

The third step in the pathway utilizes dopamine-β-hydroxylase (DBH) to convert dopamine to NE. DBH is a copper-containing enzyme that uses ascorbic acid (vitamin C) as a cofactor and is located in the membrane of the storage vesicle. Thus, as DA is actively transported into the vesicle, it gets converted to NE.[1] Inhibition of DBH within the NE terminal would, therefore, reduce the levels of NE without affecting the levels of DA. Apparently, there is some soluble DBH inside the vesicle that is coreleased with NE. In the adrenal medulla and in some neurons of the brain, NE is further

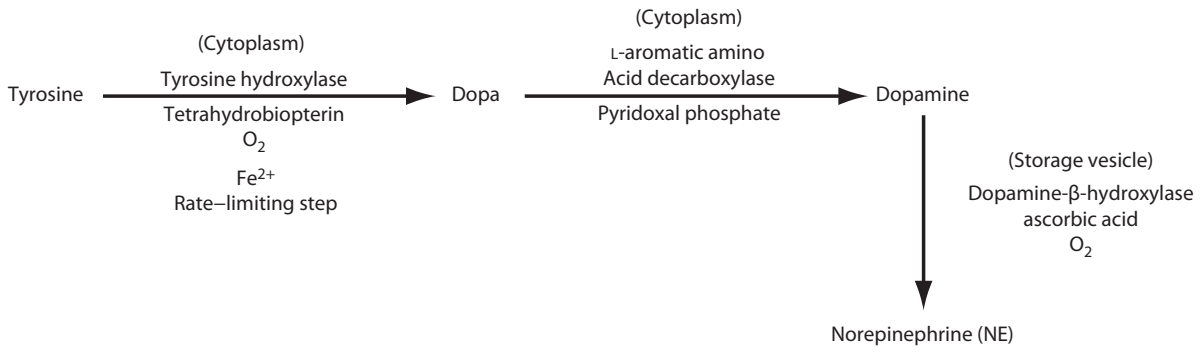

Figure 16.4 Synthesis of NE in the noradrenergic nerve terminal—the enzymes and cofactors required for synthesis as well as their location (see parentheses) within the neuron.

converted to Epi by the enzyme phenylethanolamine-*N*-methyltransferase (PNMT), which is found in the cytoplasm of cells.[16] Synthesis of NE within a neuron is regulated by a wide variety of factors, including the intracellular concentration of NE and the firing rate of the neuron.

Once synthesized, the catecholamines (NE, DA, and Epi in the brain) are stored in both small (200 to 300 Å) or large (500 to 1200 Å) membrane-bound vesicles. Inside the vesicle, NE is stored in a complex with ATP as shown in Figure 16.5. In addition to vesicular synthesis, NE in neuron terminal cytoplasm is actively transported into synaptic vesicles by an ATP-Mg^{++} dependent process[62] utilizing a *vesicular monoamine transporter* (VMAT). Uptake of NE into the vesicle by VMAT is inhibited by the drug *reserpine*, which ultimately leads to the depletion of the tissue content of NE.

The release of NE from nerve terminals occurs when the terminal is depolarized by the incoming AP. This results in the opening of voltage-dependent Ca^{2+} channels and triggers the process of exocytosis, similar to the release of ACh described previously.

Many drugs can facilitate the release of NE from nerve endings to increase the concentration in the synaptic cleft

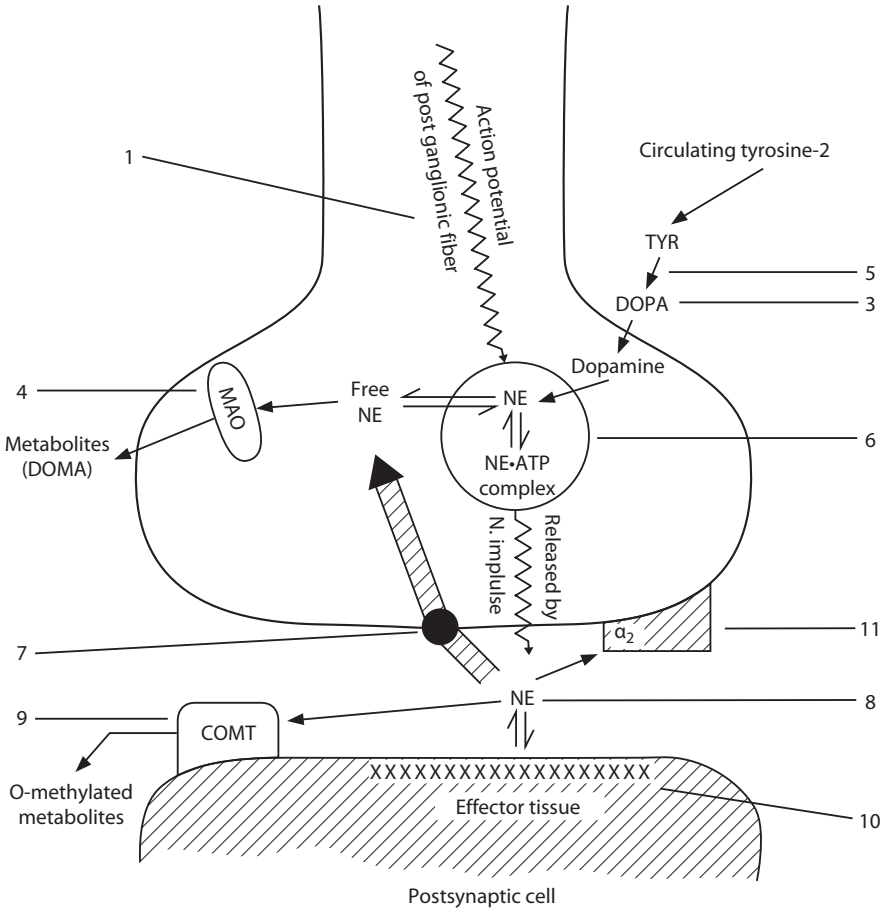

Figure 16.5 Drawing of adrenergic (sympathetic) neuron terminal synapsing on an effector organ in the peripheral ANS. This also serves as a model for adrenergic synapses in the CNS. The numbers in this model indicate the various sites at which drugs are known to act to modify neurotransmission. These are as follows: 1) some drugs (e.g., guanethidine and bretylium) inhibit release by blocking the propagation of the action potential (essential for release) into the nerve terminal; 2) under conditions of stress, it may be possible to increase NE synthesis by increasing the concentration of circulating tyrosine (i.e., by administering tyrosine); 3) a more effective way to increase DA and NE synthesis is to administer the precursor L-DOPA because it bypasses the rate-limiting step involving tyrosine hydroxylase; 4) inhibitors of monoamine oxidase (MAO; e.g., tranylcypromine) act at site 4 to prevent the degradation of NE; 5) inhibitors of tyrosine hydroxylase (e.g., alpha-methyltyrosine) act here to block synthesis of NE; 6) drugs that interfere with the storage of NE (e.g., reserpine) act on the vesicle and eventually deplete the neuron of NE; 7) drugs that block reuptake (e.g., cocaine and tricyclic antidepressants) act to increase the concentration of NE in the synapse, effectively increasing the effect of NE on postsynaptic receptors; 8) similar to NE, certain drugs can act as agonists for alpha or beta adrenergic receptors; 9) inhibitors of catechol-O-methyltransferase (COMT), an enzyme that also catabolizes NE, also can increase the availability of NE for agonist action; 10) noradrenergic receptor antagonists can also act to block the response to NE; 11) last, presynaptic alpha-2 noradrenergic receptors (autoreceptors) when activated by NE or selective drugs, such as clonidine, have the capacity to decrease the further release of NE from noradrenergic terminals.

and, thus, availability to postsynaptic receptors. These include the *amphetamines* (e.g., dextroamphetamine, Adderall®) and *methylphenidate* (Ritalin®), which stimulate the release of NE and DA by a Ca^{2+}-independent mechanism that does not involve exocytosis. In this regard, amphetamine causes a more robust release of NE than does methylphenidate.[1]

Following release of NE into the synaptic cleft and interaction with the postsynaptic receptors, the neurotransmitter action is terminated primarily by reuptake into the presynaptic terminal from which it was released. Uptake from the synaptic cleft is carried out by a protein called the *norepinephrine transporter* (NET).[1,60] The NET transports NE along with sodium (cotransporter), a process that is inhibited by *antidepressants* (tricyclic antidepressants, e.g., desipramine), *amphetamine*, and *cocaine*, but not by drugs such as reserpine (which inhibit VMAT). The molecular characteristics of NET have been studied in great detail, and the chemical structure of this protein has been determined from cloning experiments.[63] Although reuptake has been shown to be the major process responsible for terminating the action of NE, enzymatic degradation also takes place via the enzymes MAO and COMT.

MAO, which is present in the outer membrane of the mitochondrion, is involved in the intraneuronal degradation of free NE that is present in the cytoplasm of neurons (i.e., after uptake). The MAO that is found in human and rat brain is present in two forms that are referred to as *Type A* and *Type B*, based on the fact that they have different substrate specificity and different sensitivity to specific inhibitors. For further discussion of the different types of MAO, the reader is referred to Iversen et al.[1] COMT is present in most cells of the body and takes care of the extraneuronal metabolism of catecholamines (NE and DA) before they reach the urine.[1,60]

Drugs that act as inhibitors of MAO cause elevations in the intraneuronal content of catecholamines (NE and DA) as well as serotonin and eventually enhance the concentration of neurotransmitter reaching the receptors. Thus, MAO inhibitors are employed as antidepressant drugs. In addition, MAO inhibitors along with COMT inhibitors are used in the treatment of Parkinson's disease to reduce the peripheral metabolism of levodopa and enhance its concentration in the CNS. The metabolic (degradation) products resulting from the action of COMT and MAO on NE and DA are shown in Figure 16.6. These by-products represent clinically important metabolites that can be measured in cerebrospinal fluid (CSF) or urine to provide an index of how the catecholamine systems have been altered by disease or drug treatment.[60]

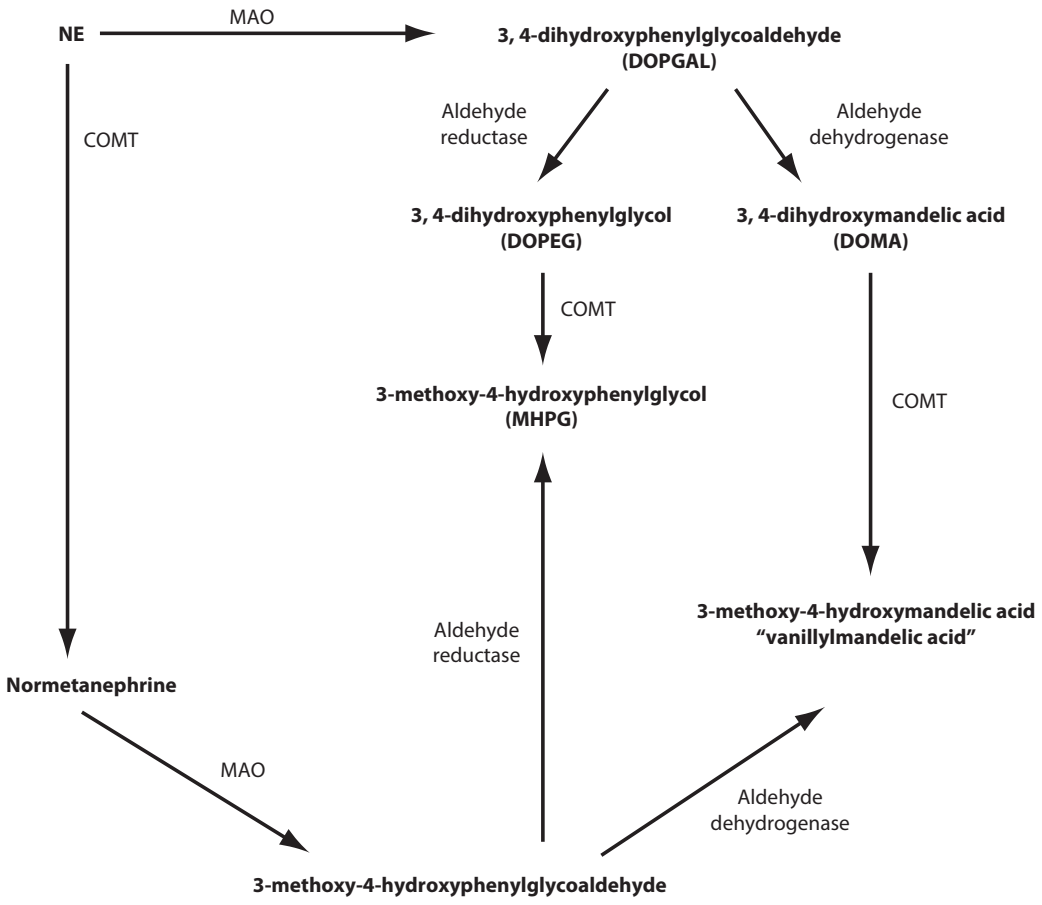

Figure 16.6 Enzymatic degradation of NE by MAO and COMT.

Norepinephrine receptors

Norepinephrine receptors (adrenoceptors) mediate the effects of NE. Adrenoceptor subtypes that respond to NE include alpha$_1$, alpha$_2$, and beta$_1$. Beta$_2$ receptors have a lower affinity for NE but have a high affinity for Epi and are involved in mediating some of the effects of the latter neurotransmitter or hormone. Specific agonists and antagonists exist for each receptor, and some of these are described later in this chapter. NE can also activate beta3 receptors found in fat cells to enhance lipolysis and in the urinary bladder where they cause bladder relaxation.

In recent years, a great deal of information has been gained about the molecular nature of the adrenoceptors, both in terms of their coupling to second messenger systems (so-called *signal transduction mechanisms*) and their chemical structure. Each receptor is known to be an integral membrane protein with seven transmembrane-spanning regions and a molecular weight of 64,000 to 80,000 Da.[64]

Unlike the nicotinic ACh receptor, which is an ion channel and produces ultrarapid effects, the adrenoceptors mediate their effects through GPCRs similar to the muscarinic ACh receptor.[16,60,61] Both beta$_1$ and beta$_2$ adrenoceptors are linked to adenylate cyclase in the membrane by a G$_s$ (*stimulatory*) protein. The alpha subunit of the G$_s$ protein (with GTP bound to it) then interacts with adenylate cyclase and activates it, leading to the conversion of ATP to cyclic AMP. The latter can, in turn, activate various protein kinases involved in the phosphorylation (i.e., the addition of a phosphate group or PO_4^-) of various proteins that regulate membrane ion transport to alter membrane potentials (Figure 16.7).

The alpha$_2$ adrenoceptors, which are usually located presynaptically (Figure 16.5), also mediate their effect on membrane potential through a G-protein and adenylate cyclase activity, but unlike the beta receptors, the alpha$_2$ receptor is linked to a G$_i$ (*inhibitory*) protein, which causes an inhibition of adenylate cyclase and a reduction in the amount of cAMP (and, presumably, a reduction in protein phosphorylation) in the neuron.

The alpha$_1$ adrenergic receptor mediates its action through another second messenger system, which is linked

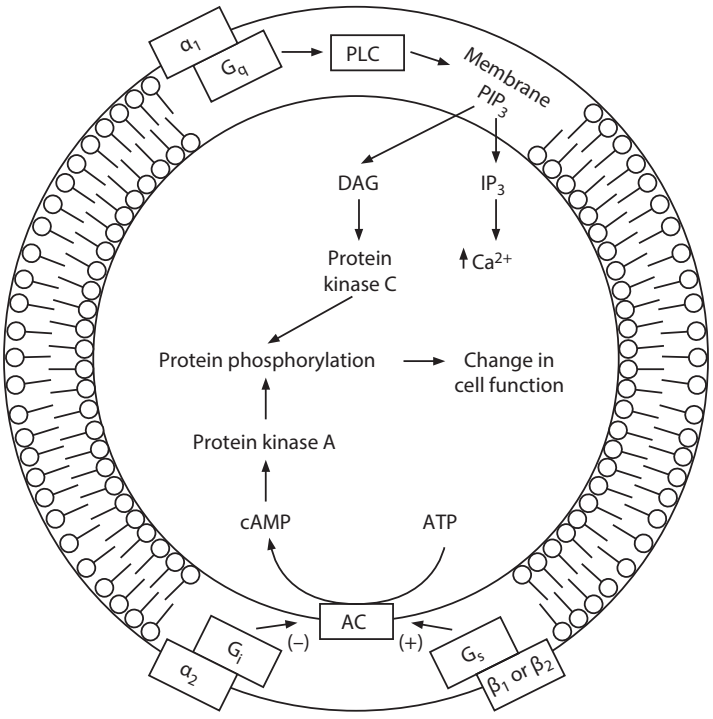

Figure 16.7 Diagram of second messenger (signaling) system linked to alpha- and beta-adrenergic receptors in a cell (neuron or effector cell) containing such receptors. The α1 receptor is linked by a G-protein (Gq) to phospholipase C (PLC), which, when activated (by agonist binding to the α1 receptor), leads to the breakdown of phosphatidylinositol 4,5-bisphosphate (PIP2) to form two second messengers (DAG and inositol triphosphate, or IP3). The DAG activates protein kinase C, which can, in turn, phosphorylate proteins, including those in ion channels. IP3 causes an increase in intracellular calcium by releasing it from various stores. Elevated calcium can, in turn, activate calcium/calmodulin-dependent protein kinase, which can also phosphorylate other proteins. Beta1 and beta2 receptors act through a G$_s$ protein to stimulate adenylyl cyclase (AC), leading to an increase in the formation of cyclic adenosine monophosphate (cAMP), which can activate protein kinase A to increase the phosphorylation of various proteins. Note that the α2 receptor acts through a G$_i$ protein (inhibitory G-protein), which leads to inhibition of AC and a decrease in the intracellular concentration of cAMP. As can be seen here, protein phosphorylation is the major mechanism by which receptors act through signal transduction to alter cell function.

to the receptor by a G_q protein. The second messengers produced when an agonist binds to the alpha$_1$ receptor are actually metabolites of phosphoinositide breakdown mediated by PLC and include IP3 and DAG as was the case for certain muscarinic receptors described previously. IP3 causes the release of Ca^{2+} from intracellular storage sites, and the Ca^{2+} can then activate protein kinases to produce phosphorylation of membrane proteins (Figure 16.7). The DAG activates protein kinase C, which, in turn, phosphorylates various proteins to mediate various cellular responses of alpha$_1$ agonists.[1,65]

Three subtypes of alpha$_1$ receptors (e.g., α_{1a}, α_{1b}, α_{1d}) and three subtypes of alpha$_2$ receptors (α_{2a}, α_{2b}, and α_{2c}) have been identified.[66] There are also three subtypes of beta receptor (β_1, β_2, and β_3). Selective agonists and/or antagonists are available for alpha$_1$, alpha$_2$, beta$_1$, beta$_2$, and beta$_3$ receptors, and these drugs are primarily used for their effects on the peripheral ANS, especially in the areas of cardiovascular or urinary tract disease. Chronic treatment with agonists or antagonists can result in compensatory changes in the sensitivity and/or receptor number of adrenergic receptors. Such changes appear to be carried out by enzymes that phosphorylate the receptor (i.e., receptor kinases).[66]

Clinically useful drugs that alter noradrenergic neurotransmission

FACILITATORS OF NORADRENERGIC NEUROTRANSMISSION

Adrenergic agonists

These are also referred to as *direct-acting sympathomimetic amines*, and they are classified as either alpha or beta agonists. There are both alpha$_1$ and alpha$_2$ agonists available, but many are nonselective. *Norepinephrine* (Levophed®) itself is available and is an agonist for alpha$_1$, alpha$_2$, and beta$_1$ receptors, and epinephrine is an agonist for all adrenergic receptors. *Phenylephrine* is an alpha$_1$ agonist that is used in nose drops (Neo-Synephrine®) as a nasal decongestant that acts to vasoconstrict the mucosal blood vessels and reduce congestion. Other alpha agonists that are predominantly alpha$_1$ selective include *methoxamine* and *metaraminol*. *Clonidine* (Catapres®) is an alpha$_2$ agonist used as an antihypertensive agent because of its action on the brain with which stimulation of alpha$_2$ receptors decreases the activation of the peripheral sympathetic nervous system. Other alpha$_2$ agonists include *guanfacine* (Tenex®) and *guanabenz* (Wytensin®).

Isoproterenol (Isuprel®) is a beta agonist that stimulates both beta$_1$ and beta$_2$ receptors and has been used as a bronchodilator because of the beta$_2$ receptors in the bronchioles that mediate bronchiolar relaxation (Table 16.3). Indeed, most of the beta agonists are used for the treatment of diseases that are associated with bronchoconstriction, such as asthma. Selective beta$_2$ agonists are also available and have the advantage of not causing cardiac stimulation when used in asthma. These include *metaproterenol* (Metaprel®), *terbutaline* (Brethine®), and *albuterol* (Proventil®). There are no highly selective beta$_1$ agonists available. However, dopamine and *dobutamine* (Dobutrex®) are used for their ability to stimulate beta$_1$ receptors in the heart to increase cardiac output in states of shock or heart failure.

Drugs that block NE reuptake

Inasmuch as reuptake (via NET) is the major mechanism for inactivating released NE, drugs that block this process have a marked ability to facilitate noradrenergic neurotransmission. The classical example of a drug that does this is *cocaine*. Cocaine, however, also blocks dopamine and serotonin reuptake. Many of the antidepressant drugs (so-called *tricyclic antidepressants*) are potent and selective inhibitors of NE uptake and, presumably, mediate some of their beneficial effects in depression via this mechanism.[67] Selective NE uptake inhibitors include *desipramine* (Norpramin®), *protriptyline* (Vivactil®), *nortriptyline* (Aventyl®), *maprotiline* (Ludiomil®), and *atomoxetine* (Strattera®). All of these are used to treat depression, except for atomoxetine, which is used to treat attention deficit hyperactivity disorder (ADHD). Side effects of these drugs include their ability to increase heart rate and blood pressure due to peripheral effects on the cardiovascular system. At plasma concentrations that exceed the recommended level, these drugs can also lower the seizure threshold and may precipitate seizures. However, therapeutic plasma levels have been shown to exert anticonvulsant effects in experimental animals.

Drugs that increase NE release

Several drugs are available to increase the release of NE (as well as dopamine in CNS) from nerve endings. The mechanism by which this is accomplished is not entirely clear. However, it appears to involve the release of NE from a nonvesicular pool that does not require calcium and does not involve exocytosis. The current hypothesis is that these drugs are taken up into the cytosol of the nerve by NET. Then, the drug (e.g., amphetamine) enters the vesicle and causes the release of NE back into the cytosol. This elevates cytosolic NE in the terminal, which then causes a reverse transport of NE by NET. Moreover, amphetamine blocks MAO, preventing the cytoplasmic degradation of NE, thus making it more available for reverse transport.[16] Drugs that facilitate the release of NE by these mechanisms include *amphetamine*, *dextroamphetamine* (Dexedrine®), *methamphetamine* (Desoxyn®), and *methylphenidate* (Ritalin®). These drugs also increase the release of dopamine from nerve terminals, which is believed to be responsible for many of their effects and is discussed later.

Amphetamine is the racemic mixture of D- and L-amphetamine. Dextroamphetamine is three to four times more potent in stimulating the CNS than is L-amphetamine. One commercial product contains a mixture of amphetamine and dextroamphetamine (Adderall®). All amphetamine analogs have powerful cardiovascular stimulating effects, leading to an increase in blood pressure and the work of the heart. The CNS-stimulating effects of amphetamine

on arousal and locomotor activity are dependent on newly synthesized NE or dopamine because these effects are blocked by alpha methyltyrosine, a tyrosine hydroxylase inhibitor used to block NE synthesis.[42]

The amphetamines, as a group, are used to suppress appetite in the treatment of obesity and to treat narcolepsy (a sleep disorder) and ADHD. These drugs are regulated as controlled substances because of their abuse potential. High doses can produce a psychosis that is indistinguishable from an acute paranoid schizophrenic syndrome. Moreover, it has been shown, in both rats and nonhuman primates, that repeated injections of methamphetamine can produce neurotoxicity leading to the loss of both dopamine and serotonin-containing neurons in the brain.[68–71] The mechanism responsible for this neurotoxicity remains unknown although several hypotheses have been proposed.

Drugs that decrease the enzymatic degradation of NE

NE is degraded intraneuronally by the enzyme MAO as indicated previously. Inhibiting this enzyme should eventually increase the concentration of NE in the synaptic cleft. Several nonselective MAO inhibitors are used clinically as antidepressants. These include *tranylcypromine* (Parnate), *phenelzine* (Nardil®), and *isocarboxazid* (Marplan®). *Selegiline* marketed as a transdermal patch (Emsam®) is a selective MAO-B inhibitor that is FDA-approved for the treatment of depression. Selegiline marketed as Eldepryl® is also used for Parkinson's disease (but not depression). Rasagiline (Azilect®) is another MAO-B inhibitor used for the treatment of Parkinson's disease. Patients on MAO inhibitors, particularly those that contain MAO-A, cannot eat foods containing tyramine, a potent NE releaser. Normally, tyramine is metabolized by MAO in the intestine, but this enzyme is inactive in patients on an MAO-A inhibitor. Tyramine reaching the circulation causes a hypertensive crisis with very dangerous consequences. Thus, individuals taking MAO inhibitors must avoid foods containing tyramine, such as wine, beer, cheese, and other fermented products.

INHIBITORS OF NORADRENERGIC NEUROTRANSMISSION

Adrenoceptor antagonists

There have long been available drugs that are selective antagonists of either alpha or beta adrenergic receptors. Now, we have drugs that are even selective for a specific subtype of alpha or beta receptor. The main advantage of a subtype selective antagonist is that it will have fewer side effects. Nonselective alpha antagonists include *phenoxybenzamine* (Dibenzyline®) and *phentolamine* (OraVerse®), and nonselective beta antagonists include *propranolol* (Inderal®), *sotalol* (Betapace®), and *pindolol* (Visken®). Of interest for the treatment of hypertension are the $alpha_1$ selective antagonists *prazosin* (Minipress®), *doxazosin* (Cardura®), and *terazosin* (Hytrin®). $Beta_1$ selective antagonists are useful because they can be used to reduce blood pressure, stop cardiac arrhythmias, or prevent subsequent heart attacks with minimal effects on bronchiolar smooth muscle. *Metoprolol* (Lopressor®), *atenolol* (Tenormin®), *acebutolol* (Sectral®), and *esmolol* (Brevibloc®) are all currently marketed $beta_1$ selective antagonists used to treat cardiovascular disorders.

Inhibitors of NE release

Some drugs are selectively taken up into noradrenergic nerve terminals and then prevent the release of NE, apparently by blocking the invasion of the AP into the terminal (i.e., a local anesthetic-like effect). Drugs in this category are referred to as *adrenergic neuronal blocking agents* and include *guanethidine* (Ismelin®), *guanadrel* (Hylorel®), and *bretylium tosylate*. Initially, these drugs cause a transient release of NE prior to the inhibition of release. When used chronically, guanethidine also has a reserpine-like effect (see the following) by interfering with NE storage and depleting the neurons of NE. Such drugs have primarily been used as antihypertensive agents in the past but are rarely used today.

Inhibitors of NE storage

Reserpine is the classical drug for inhibiting the storage of catecholamines (NE, Epi, and DA) and serotonin (see the following text). Reserpine binds irreversibly to the vesicle membrane and interferes with the VMAT-mediated uptake of monoamines into the vesicle,[1] rendering the vesicle nonfunctional. When NE cannot be stored in the vesicle, it is not protected and is degraded by MAO. Thus, reserpine leads to a depletion of the NE from the nerve terminals. It is primarily used in combination with other drugs as an antihypertensive agent.[72] *Tetrabenazine* (Xenazine®) is similar to reserpine but binds reversibly to VMAT and therefore has a shorter duration of action. Tetrabenazine is approved for the use in Huntington disease to deplete striatal DA and reduce hyperkinesia.[73]

Inhibitors of NE synthesis

There are two sites within the NE synthetic pathway where drugs can be used to block synthesis: 1) the tyrosine hydroxylase step (which is the rate-limiting enzyme) and 2) the dopamine β hydroxylase step. The latter is more selective and can be accomplished with the drug *disulfiram* (Antabuse®) or its active metabolite diethyldithiocarbamate (DDTC). Unfortunately, these drugs inhibit many other enzymes and have many side effects. The most common way to interfere with synthesis of NE is to inhibit tyrosine hydroxylase with α-methyltyrosine (*metyrosine*, Demser®). However, this drug also blocks the synthesis of epinephrine and dopamine and is, therefore, not very selective.

Noradrenergic drugs in the TBI patient

There is considerable evidence that enhancing noradrenergic neurotransmission in the CNS has beneficial effects on recovery of function after TBI in animal studies.[74–78]

Moreover, interference with noradrenergic neurotransmission (e.g., using alpha adrenoceptor antagonists) was found to retard the recovery of motor function in rats after head injury.[79] Because of these findings, Feeney and coworkers[75] have put forth the NE hypothesis of recovery. Consistent with this hypothesis is the finding that amphetamines, when paired with physical therapy, have been shown to enhance recovery following stroke.[80,81]

The above findings indicate that drugs that enhance CNS NE neurotransmission (e.g., *d*-amphetamine, tricyclic antidepressants) may facilitate recovery following TBI. Importantly, the catecholamines also play a significant therapeutic role in acute care of the severe TBI patient, especially regarding hemodynamic homeostasis and maintenance of cerebral perfusion pressure. Here, peripheral sympathomimetics are commonly used with volume expansion to maintain cerebral vascular perfusion. However, as reviewed by Stover et al.,[82] this clinical practice is not without risk and must be balanced in consideration of several peripheral organs (and systems) that are also "catecholamine sensitive." For example, NE-induced pulmonary vasoconstriction and venous congestion may induce pleural effusion; NE can aberrantly activate cells of the immune system and promote thrombocyte-neutrophil aggregation participant in multiorgan failure, etc. Thus, although intended to be therapeutically beneficial regarding brain health following TBI, there are numerous possibilities (theoretical and otherwise) of unintended and perhaps debilitating consequences with catecholamine-based therapy in severe TBI. Certainly, because much of the "recovery" data has been obtained in carefully controlled animal studies, more clinical studies are needed on the role of NE in the recovery of brain function after insult and the concomitant effects on other body systems.

DOPAMINE

Dopamine (DA) can be found in the PNS in such places as the carotid body and sympathetic ganglia; however, it is of interest primarily for its neurotransmitter role in the CNS where it is involved in a wide variety of functions, such as regulating motor function (basal ganglia), higher cognitive functions (e.g., working memory), addictive behaviors, and inhibiting the release of prolactin from the anterior pituitary gland. Most of the DA neurons in the brain have their cell bodies either in the midbrain (e.g., substantia nigra and ventral tegmental area) where they are involved in the regulation of emotional states or motor activity (e.g., substantia nigra dopamine is lost in Parkinson's disease) or the hypothalamus where it is involved in regulating endocrine function.[1] There are three major dopaminergic pathways in the CNS: 1) the nigrostriatal pathway (which projects from substantia nigra to the striatum and is important in Parkinson's disease), 2) the mesocortical/mesolimbic system (which projects from the ventral tegmental area [VTA] of the midbrain to the limbic system and the cerebral cortex, playing a role in psychiatric disorders), and 3) the tuberoinfundibular pathway (which projects from the arcuate nucleus of the hypothalamus to the median eminence of the pituitary stalk and regulates endocrine function). Several lines of evidence, both experimental and clinical, suggest that perturbations in dopaminergic functions accompany severe TBI and may be a cause of long-term problems[83,84] not the least of which is an increased risk of Parkinson's disease (discussed in the following). First, however, we review the physiology and pharmacology of DA.

Synthesis, storage, release, and inactivation of dopamine

Dopamine is an intermediate compound in the synthesis of NE and is, in fact, the immediate precursor of NE (see Figures 16.4 and Figure 16.8). Thus, the synthesis is identical to that of NE up through the formation of dopamine but does not proceed to NE because dopaminergic neurons lack the enzyme dopamine-β-hydroxylase. As was the case with NE synthesis, tyrosine hydroxylase is the rate-limiting enzyme in the synthetic pathway and, if one wants to block synthesis, this is the enzyme to block.

Dopamine synthesis is regulated somewhat differently than is NE synthesis. This is largely because dopaminergic neurons have autoreceptors on the dopamine nerve terminal that regulate both synthesis and release whereas NE neurons have autoreceptors (which are α_2) that regulate release only.[1] However, like NE, the intracellular concentration of dopamine can regulate synthesis through end-product inhibition. Again, tyrosine hydroxylase is normally saturated with tyrosine so that administering tyrosine is not an effective way to enhance the synthesis of dopamine. However, DOPA decarboxylase is not saturated with substrate and synthesis of dopamine can be increased by the administration of DOPA, given as *levodopa*, which is now the drug of choice in the treatment of Parkinson's disease. In Parkinson's disease, the nigrostriatal dopaminergic pathway progressively degenerates, and the administration of levodopa helps replace the DA in the striatum.

Dopamine is stored in synaptic vesicles in a manner similar to that of NE in a complex with ATP. Several soluble proteins called *chromogranins* are also present in the DA synaptic vesicle. The release of DA from nerve terminals, such as that of NE, is triggered by the arrival of an action potential. Release occurs by a process of exocytosis and, therefore, is calcium-dependent. The release of DA is apparently reduced by a negative feedback mechanism when excess dopamine in the synaptic cleft interacts with presynaptic receptors (autoreceptors). Activation of autoreceptors on the cell body reduces the firing rates of dopaminergic neurons.[1] All dopaminergic autoreceptors are believed to be of the D_2 or D_3 subtype (see Dopamine Receptors section).

Dopamine is inactivated following release by a high-affinity uptake transporter called the *dopamine transporter* (DAT), which transports it back into the neuron from which it was released. This is an energy-requiring process that is dependent on sodium and is similar to the NE

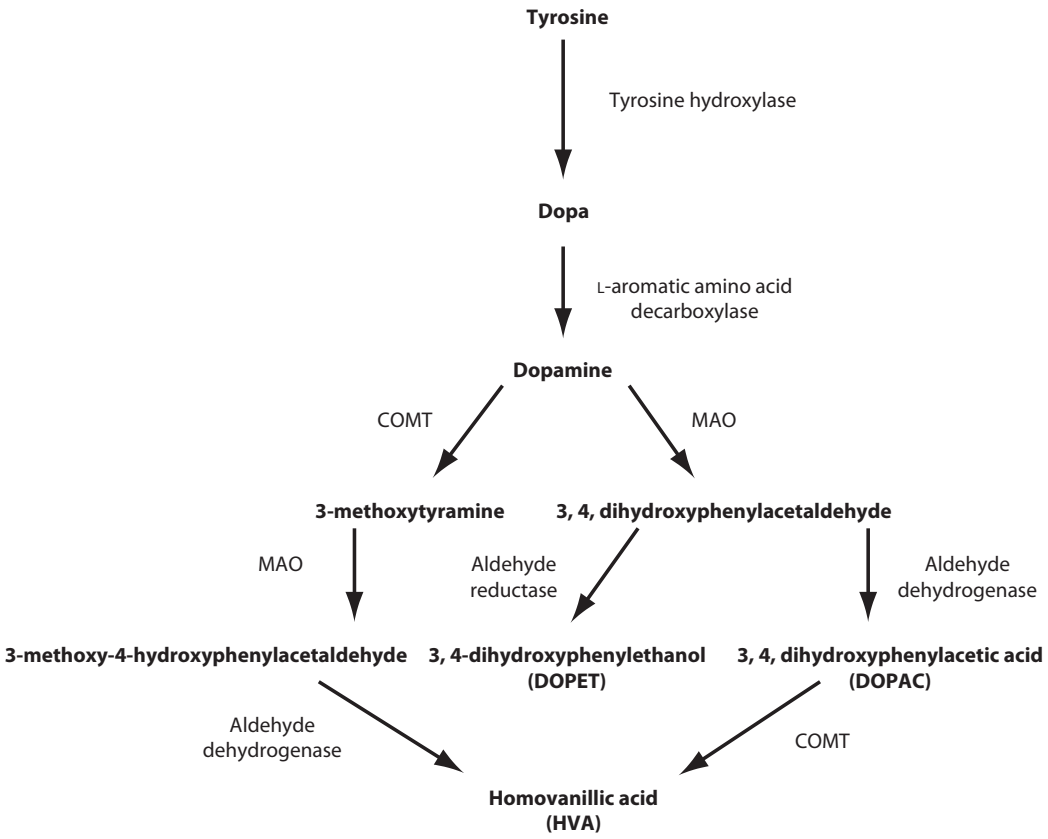

Figure 16.8 Synthesis and degradation of dopamine. Note that HVA is the major metabolite. COMT: catechol-*O*-methyltransferase; DOPA: dihydroxyphenylalanine; MAO: monoamine oxidase.

reuptake via NET. As is the case with NET and most other neurotransporters, DAT has been cloned and found to be a member of a large family of transporter proteins that have 12 membrane-spanning regions. Indeed, much is known about the molecular characteristics of the DA transporter.[85]

Although reuptake into the neuron from which it was released is the primary mechanism for terminating the physiological effects of released DA, it may also undergo enzymatic metabolism (degradation) similar to NE. Thus, both MAO and COMT can convert DA to inactive compounds according to the schema shown in Figure 16.8. Moreover, the resulting metabolites DOPAC and HVA (Figure 16.8) are often used as indices of the rate of DA turnover (rate of synthesis and degradation) in the CNS. Antipsychotic drugs (neuroleptics) that block DA receptors increase the concentration of DA metabolites in CSF and in the brain.[1]

Dopamine receptors

Two subtypes of DA receptors (D-1 and D-2) were originally identified and described using receptor-binding techniques.[86] However, using molecular cloning techniques, five DA receptors have been identified, and all of them, including the new ones (D-3, D-4, and D-5), are now classified as either D-1-like or D-2-like receptors.[87–90] The D-1-like receptors include the D-1 and D-5 receptors, and the D-2-like receptors include D-2, D-3, and D-4 receptors. The D-1-like receptors appear to mediate their effects through a G_s protein, which activates adenylate cyclase and increases cyclic AMP whereas the D-2-like receptors appear to be negatively coupled to adenylate cyclase, producing an inhibition of the latter through a G_i protein. All of the DA receptors (D-1, D-2, D-3, D-4, and D-5) are structurally typical GPCRs.

There is considerable sequence homology (a similar sequence of amino acids in the protein) between the various DA receptors as well as between these receptors and other members of this family, such as the $beta_1$ and muscarinic receptors.[87] The D-3 receptor appears to represent both an autoreceptor and postsynaptic receptor and is found in limbic areas of the brain.[87] For older so–called *typical antipsychotic* drugs, there is a high correlation between their clinical potency and their D-2 receptor blocking action. However, *clozapine* is much more potent at blocking D-4 receptors and has fewer motor side effects than the other antipsychotic drugs. Moreover, clozapine is effective at alleviating the symptoms of schizophrenia in some patients who are refractory to other antipsychotic drugs. Clozapine is also more effective against the negative symptoms of schizophrenia than are the typical antipsychotic drugs. Because of these differences, clozapine and newer antipsychotic drugs are referred to as *atypical antipsychotics*. In general, the functions of most subtypes of DA receptors are unknown; D-1 receptors have only been found postsynaptically, but

D-2 receptors occur either pre- or postsynaptically, and autoreceptors are usually of the D-2 subtype. The use of D-1 and D-2 agonists has shown that activation of both receptors may be necessary for expression of certain DA functions. Although the atypical antipsychotic drugs, such as clozapine and olanzepine, have a low affinity for the D-2 receptor, it appears that blockade of this receptor subtype is still important in their action.

The DA neurons have been implicated in the abuse of stimulants, such as cocaine and amphetamine. Mesolimbic dopaminergic neurons have also been implicated in addiction to alcohol, opioids, and nicotine. It has been proposed that variations in the gene for the D-2 receptor may contribute to interindividual differences in vulnerability to alcoholism and polysubstance abuse.[91]

Clinically useful drugs that alter dopamine neurotransmission

FACILITATORS OF DOPAMINERGIC NEUROTRANSMISSION

Dopamine agonists

Dopamine itself does not cross the blood–brain barrier and, therefore, cannot be used for effects on the CNS. However, DA is used intravenously for its effects on the cardiovascular system where it acts on $beta_1$ receptors in the heart to increase contractility and on DA receptors in the renal vasculature to cause vasodilation. Because of the latter two actions, DA is used to treat various forms of shock. *Apomorphine* is a nonselective DA agonist that does get into the brain and has been used to treat such things as Parkinson's disease. However, it is poorly absorbed from the gut and must be administered parenterally. *Apomorphine* (Apokyn®) is now available in an injectable form (subcutaneous) for the rescue from the "off phenomenon" in patients with advanced Parkinson's disease.[92] When apomorphine is used in patients, it is given with an antiemetic (trimethobenzamide or Tigan®). This is because apomorphine achieves high concentrations in the chemoreceptor trigger zone (CTZ) in the area postrema of the medulla oblongata, which leads to nausea and vomiting unless an antiemetic is given first. Other nonselective DA agonists include *bromocriptine* (Parlodel®), which has long been used to treat endocrine disorders, such as hyperprolactinemia, where it acts in the anterior pituitary gland to inhibit the release of prolactin. Bromocriptine is also now recommended for the treatment of Parkinson's disease. *Pergolide* (Permax®) is another DA agonist[1] that, along with bromocriptine, has been used in Parkinson's disease. However, bromocriptine and pergolide, which are ergot alkaloids, are not used much because of possible heart valve damage. Only bromocriptine remains on the market in the United States.

Several nonergot DA agonists have been introduced for the treatment of Parkinson's disease in recent years. These include *ropinirole* (Requip®), a D-2 and D-3 agonist; *pramipexole* (Mirapex®), also a D-2 and D-3 agonist; and *rotigotine* (Neupro®), a D-1, D-2, and D-3 agonist.

Drugs that increase the synaptic concentration of dopamine by acting indirectly

These include the indirectly acting agents, such as *amphetamine* and *methylphenidate* (Ritalin®), which increase the release of DA (as well as NE, see previous sections) into the synaptic cleft, the DA reuptake inhibitors (amphetamine, *nomifensine*, benztropine, *amantadine*, methylphenidate), and the drugs that increase DA synthesis (*levodopa*). The reader will note that some drugs have more than one action. For example, amphetamine, methylphenidate, and amantadine increase the release of DA from nerve endings as well as prevent its inactivation by reuptake.

Drugs that block enzymatic degradation of dopamine

Like other catecholamines, DA is degraded by the enzymes MAO and COMT (see Figure 16.8). Therefore, MAO inhibitors can increase the nerve terminal concentration of DA and, thus, the amount released. Selegiline (Eldepryl®, described previously) as well as rasagiline (Azilect®) are now being used to treat Parkinson's disease because they prevent the enzymatic degradation of DA and may prevent the formation of neurotoxins that destroy DA neurons and arrest the progression of the disease.[93] All of the MAO inhibitors described previously under NE will also prevent the enzymatic degradation of DA. Two COMT inhibitors have recently become available for the treatment of Parkinson's disease. These include *tolcapone* (Tasmar®) and *entacapone* (Comtan®), which block the conversion of levodopa to 3-*O*-methyldopa in the periphery and increase the amount of levodopa that gets converted to DA in the brain.[94]

The COMT inhibitors can reduce the "wearing off" symptoms in Parkinson's disease patients treated with levodopa/carbidopa. It should be noted that tolcapone has been removed from the market in Canada due to serious hepatotoxicity. However, it remains on the market in the United States with a black box warning.

INHIBITORS OF DOPAMINERGIC NEUROTRANSMISSION

Drugs that interfere with dopaminergic neurotransmission

In this category, we have just two groups of drugs: 1) the receptor antagonists or blockers and 2) the drugs that interfere with storage (e.g., reserpine). As would be expected, the only ones that provide selective effects on DA neurotransmission are the receptor blockers because reserpine-like drugs interfere with the storage of all monoamines. We will, therefore, consider only the DA antagonists here.

Antagonists of DA receptors are primarily used as antipsychotic drugs (also called *neuroleptics*) to treat schizophrenia. The fact that essentially all of the drugs effective in schizophrenia are DA antagonists has led to the hypothesis

Table 16.4 Dopamine receptor antagonists (blockers) used clinically

Chemical class	Examples of drugs	Receptor type
Typical Antipsychotics		
Phenothiazines	Chlorpromazine	D-1 and D-2
	Thioridazine	
	Perphenazine	
Thioxanthenes	Thiothixene	D-2
Butyrophenones	Haloperidol (Haldol®)	Some selectivity for D-2
Dihydroindoles	Molindone	D-2
Others		
Substituted benzamides	Metoclopramide (Reglan®)	D-2
Atypical Antipsychotics		
(varied chemical classes)	Clozapine (Clozaril®)	D-2, D-4, 5-HT_{2A}
	Risperidone (Risperdal®)	D-2, D-4, 5-HT_{2A}
	Olanzapine (Zyprexa®)	D-2, D-4, 5-HT_{2A}
	Quetiapine (Seroquel®)	D-2, D-4, 5-HT_{2A}
	Ziprasidone (Geodon®)	D-2, D-4, 5-HT_{2A}
	Paliperidone (Invega®)	D-2, D-4, 5-HT_{2A}
	Aripiprazole (Abilify®)	Partial D-2 agonist, 5-HT_{2A}
	Iloperidone (Fanapt®)	D-2, D-4, 5-HT_{2A}
	Anesapine (Saphris®)	D-2, D-4, 5-HT_{2A}
	Lurasidone (Latuda®)	D-2, D-4, 5-HT_{2A}

Source: Meyer, J. M., Pharmacotherapy of psychosis and mania, in Brunton, L. L., Chabner, B. A., and Knollmann, B. C., Eds., *The pharmacological basis of therapeutics*,12th Edition, McGraw-Hill, New York, 485, 2011, 417.

that schizophrenia is caused by too much DA at certain synapses—a hypothesis that has been difficult to prove. Essentially, all of the DA antagonists block D-2 receptors, but D-1 and D-4 receptors may be affected by certain drugs. The atypical antipsychotic drugs, unlike the older (typical) drugs, appear to have a low affinity for the D-2 receptor and have a higher affinity for the D-3 or D-4 receptor. The latter drugs are also effective antagonists at the serotonin 5-HT_{2A} receptor.[67] A list of the DA antagonists used clinically (most of which are antipsychotic drugs) is given in Table 16.4.

Dopamine antagonists have many side effects because they block DA receptors not only in the limbic system, which regulates emotion, but also in the basal ganglia, where loss of DA function causes Parkinsonian-like symptoms, and in the pituitary where they cause endocrine-related side effects. *Metoclopramide* (Reglan®) is a DA antagonist used for its peripheral effects and its effects on the chemoreceptor trigger zone (which is outside the blood–brain barrier) to prevent nausea and vomiting. Although it penetrates the brain poorly, some does reach the basal ganglia, which can cause some Parkinsonian-like side effects. All of the D-2 receptor antagonists have antiemetic properties, but only some (e.g., metoclopramide and *prochlorperazine* [Compazine®]) are approved for such use.

Dopaminergic drugs in the TBI patient

Several reports in recent years suggest that enhancing DA neurotransmission may be beneficial to patients with TBI. Improving dopaminergic function appears to be useful for two types of deficits in these patients. First, some TBI patients display Parkinsonian-like symptoms, and second, dopaminergic agents may improve arousal and the ability to focus attention on the task at hand and generally improve cognitive ability.[83,84] The latter effect may be mediated through the prefrontal cortex (PFC),[95] but the level (regulated by dose) of DA receptor stimulation appears to be critical because of the inverted U-shaped function of DA receptor activation in the PFC.[1,95] Just as L-DOPA (levodopa) is effective in Parkinson's disease, it may help similar symptoms in patients with TBI. The combination of L-DOPA with a peripheral decarboxylase inhibitor will reduce the metabolism of L-DOPA in the periphery and increase the amount that actually reaches the brain. Thus, the combination of *levodopa* and carbidopa (a decarboxylase inhibitor) is often used in Parkinson's disease. Sinemet® (a mixture of L-DOPA and carbidopa) has, in fact, been used successfully in some patients with TBI.[96,97] There is also some evidence from animal studies that treatment with DA agonists (e.g., ropinirole) can either reduce or reverse the motor and cognitive deficits produced by brain injury.[98]

A variety of DA agonists are also available and may have an advantage because they do not depend on intact dopaminergic neurons. The DA agonists include such things as the ergot derivatives (e.g., bromocriptine) and nonergot agonists (e.g., ropinirole, pramipexole) described previously. The antiviral drug *amantadine* may be considered to be an indirect-acting agonist. There is some evidence that these drugs can reduce fatigue, distractibility, and

bradykinesia and improve attention, concentration, and purposeful movement in TBI patients.[99,100]

The use of DA antagonists can be advantageous in controlling the symptoms of psychosis but could impair motivation and cognition. The role of dopamine neurons in motivation and reward as well as in addiction is well established.[17] Thus, blocking DA receptors could reduce motivation. Perhaps it would be possible to enhance motivation with a dopamine reuptake inhibitor such as *bupropion* (Wellbutrin®, Zyban®) or methylphenidate (Ritalin®). There are reports showing that bupropion improves restlessness and methylphenidate improves cognitive function in TBI patients.[84,101] Moreover, as expected, there is experimental evidence that DA receptor antagonists (e.g., antipsychotic drugs) can impair recovery of cognitive function after TBI.[102] Thus, having knowledge of DA neurotransmission, including receptor populations and the diverse functional circuitry through which DA acts, will promote a better understanding and rationale for DA pharmacotherapy in TBI.

5-HYDROXYTRYPTAMINE (SEROTONIN)

5-Hydroxytryptamine or serotonin (5-HT) is an indolamine that is found in both the periphery and the CNS. About 90% of the 5-HT in the body is found in the gastrointestinal tract (in enterochromaffin cells and neurons of the myenteric plexus), 8% of the 5-HT of the body is found in platelets, and only 2% is found in the brain.[1] It is, however, the 2% in the brain that receives most of the attention, and this is the fraction we focus on. Nevertheless, there are 5-HT receptors throughout the body, and many side effects of serotonergic drugs used for an action in the CNS are mediated via the peripheral effects. Sometimes, the serotonergic drugs are used clinically for their peripheral effects, such as the use of 5-HT_3 antagonists for the treatment of irritable bowel syndrome.

Within the brain, 5-HT is localized in neurons that express the gene for tryptophan hydroxylase (TPH). Extensive mapping of serotonergic neurons in the CNS of the rat has been performed using fluorescence histochemistry and immunocytochemistry. In general, the cell bodies of the serotonergic neurons are located along the midline of the brain stem in what are called *raphe nuclei*. Originally, nine separate groups of 5-HT cell bodies were described by Dahlstrom and Fuxe,[103] but more recently, other cell groups have been detected in the area postrema (vomiting area) and in the caudal locus coeruleus as well as in the interpeduncular nucleus.[1] Like the noradrenergic neurons, the serotonergic neurons have a widespread terminal distribution innervating essentially all areas of the CNS from the cerebral cortex to the spinal cord. The more caudal cell groups (B-1 to B-3) primarily innervate the brain stem and spinal cord, and the rostral cell groups (B-6 to B-9) innervate the forebrain. A detailed description of the neuroanatomy of serotonergic neurons has been provided by Molliver.[104]

Synthesis, storage, release, and inactivation of serotonin

The amino acid precursor for 5-HT synthesis is tryptophan, which is an essential amino acid supplied in the diet. Tryptophan, like tyrosine, is a neutral amino acid that also gains entry into the brain by the large neutral amino acid transporter. Thus, plasma tryptophan will compete with other neutral amino acids, such as tyrosine and phenylalanine, for transport into the brain. Accordingly, the concentration of brain tryptophan will be determined not only by the concentration of tryptophan in plasma but also by the plasma concentration of other neutral amino acids.[1,105] Once in the extracellular fluid of the brain, tryptophan is transported into the serotonergic neurons by a high-affinity and a low-affinity transport system in which it can then be converted to 5-HT by a two-step reaction (Figure 16.9) with each step being catalyzed by a different enzyme.[106]

The rate-limiting step in the overall conversion of tryptophan to serotonin is the first step that is catalyzed by TPH (Figure 16.9) and results in the conversion of tryptophan to 5-hydroxytryptophan (5-HTP). Like tyrosine hydroxylase, tryptophan hydroxylase is a cytoplasmic mixed-function oxidase that requires molecular oxygen and a reduced pteridine as cofactors. It should also be noted that a membrane-associated form of tryptophan hydroxylase has been found, indicating that some of the enzyme may be membrane bound. Two isoforms of tryptophan hydroxylase (tryptophan hydroxylase-1 and tryptophan hydroxylase-2) have been identified. Tryptophan hydroxylase-2 (TPH2) is the one that is expressed primarily in the brain.[107] Polymorphisms (alterations) in the gene that codes for TPH2 may be associated with altered susceptibility to affective disorders (e.g., depression) and one's responsiveness to antidepressants.[1] Various inhibitors of tryptophan hydroxylase have been identified, the best known of which is parachlorophenylalanine (PCPA), which has been used experimentally to study the function of 5-HT.

Inasmuch as the K_m of tryptophan hydroxylase (50 to 120 μM) is higher than the concentration of brain tryptophan (30 μM), the enzyme is not saturated with tryptophan, which means that increasing the concentration of brain tryptophan can increase the synthesis of 5-HT and lead to higher brain levels of serotonin.[106,108] Thus, it has been found that dietary manipulations of tryptophan can change the brain concentration of serotonin. The 5-HTP formed by the action of TPH2 on tryptophan is immediately converted to 5-HT (serotonin) by the action of L-aromatic amino acid decarboxylase, the same enzyme that converts DOPA to dopamine in catecholaminergic neurons. The decarboxylation of 5-HTP, like that of DOPA, requires pyridoxal phosphate as a cofactor. Inasmuch as the decarboxylation takes place in the cytoplasm, the resulting 5-HT must then be transported into vesicles for storage (see following text).

The rate of 5-HT synthesis appears to be regulated by the rate of neuronal firing. The latter control over 5-HT

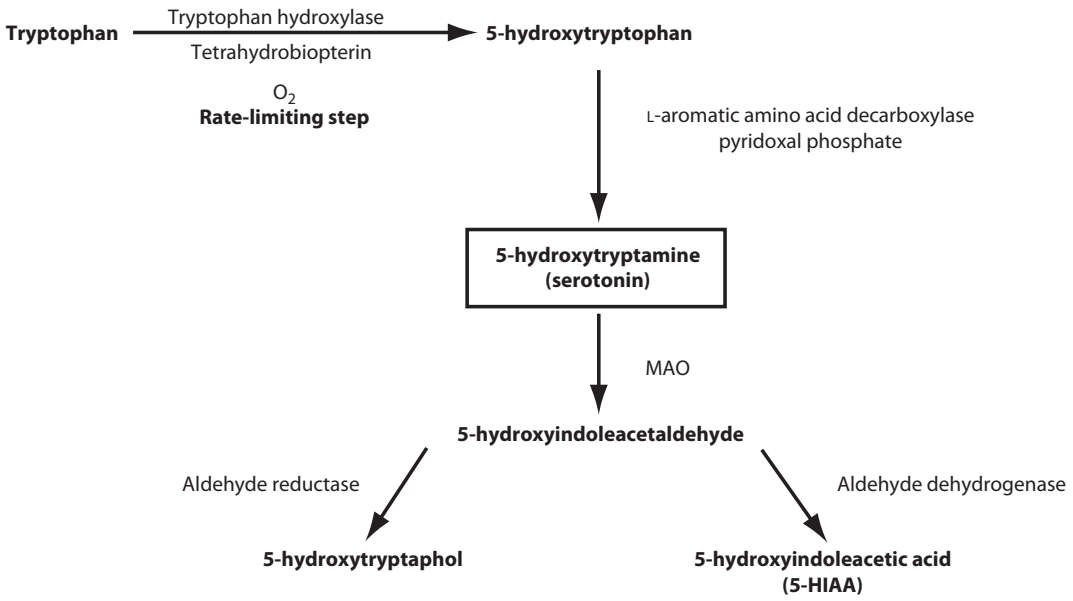

Figure 16.9 Synthesis and degradation of 5-hydroxytryptamine (serotonin) in the CNS. Note that 5-HIAA is the major metabolite. MAO: monoamine oxidase.

synthesis appears to be exerted on tryptophan hydroxylase by a Ca^{2+}-dependent phosphorylation of this rate-limiting enzyme.[108]

Serotonin, like the catecholamines, is stored in synaptic vesicles inside nerve terminals.[109] These vesicles have been shown to take up serotonin from the cytoplasm via the same VMAT (VMAT-2) that transports catecholamines.[110–112] Release of 5-HT, like that of other neurotransmitters, appears to occur by exocytosis in a calcium-dependent manner.[109] However, certain drugs, such as *p-chloroamphetamine* and *fenfluramine* (not clinically available), are believed to release serotonin from the cytoplasmic pool rather than the vesicular pool,[113] and there is some evidence that the depolarization-mediated release by neurons can involve either vesicular or cytoplasmic pools.[114] Unlike catecholamine-containing vesicles, serotonergic synaptic vesicles do not contain ATP but do contain a protein that strongly binds serotonin in the presence of iron (Fe^{++}), called serotonin-binding protein (SBP).[108,109] SPB is released from neurons along with 5-HT in a calcium-dependent manner.[108]

The release of 5-HT from nerve endings is also regulated via a negative feedback mechanism through serotonin autoreceptors located on the presynaptic (serotonergic) nerve terminals. The evidence indicates that these 5-HT autoreceptors are of the 5-HT_{1B} or $_{1D}$ subtype, depending on the animal species (see following text).[108]

Mechanisms similar to those of catecholamine inactivation (see previous text) have been shown to occur for serotonin inactivation. Reuptake into the neuron from which it was released and monoamine oxidase activity are involved in the inactivation of 5-HT following its action in the synaptic cleft. A high-affinity, sodium-dependent, energy-dependent (requires ATP) uptake of 5-HT has been demonstrated in experimental studies,[105] and reuptake into serotonergic terminals appears to function as the primary inactivation mechanism for removing 5-HT from the synaptic cleft. This uptake of 5-HT is mediated by a serotonin transporter (SERT) that has been cloned and widely studied.[1,112] There is much interest in determining whether genetic variability in SERT is associated with various psychiatric disorders. Indeed, the importance of SERT in psychiatric disease is supported by studies showing major antidepressants, such as *fluoxetine* (Prozac®), *sertraline* (Zoloft®), or *paroxetine* (Paxil®) (see SSRI drug discussion below), exert their effects by inhibiting SERT and thereby enhancing the action of serotonin. Additionally, molecular studies in mice lacking the SERT gene (referred to as *SLC5A4*) show an important role of SERT in behavioral states.[115] As indicated previously, the uptake of serotonin by SERT can be followed by degradation by monoamine oxidase to form 5-hydroxyindoleacetic acid (5-HIAA). Many investigators have suggested that brain or CSF levels of 5-HIAA can be used as an index of 5-HT turnover and utilization.[116] From Figure 16.8, it can be seen that 5-hydroxytryptophol can also be formed by the action of monoamine oxidase on serotonin in the brain although the major metabolite is 5-HIAA.[108] In addition to the primary mechanism of terminating the synaptic action of 5-HT following release from the neuron (i.e., reuptake into the neuron), it is now believed that the activity of 5-HT in the extracellular space can also be terminated by uptake into glial cells and other neurons via a low-affinity, high-capacity transport process (not via SERT). The latter process is referred to as secondary transport of 5-HT.[108]

Serotonin has been implicated in various psychiatric disorders, including depression, anxiety disorders, and

depression associated with suicide. Indeed, it is not always easy to determine what changes in 5-HT are important because they may involve opposing alterations in different subnuclei of the raphe (serotonergic neurons).[117] However, it is clear that reducing serotonergic neurotransmission in some areas of the brain can precipitate depressive episodes in some patients whereas restoring a downregulated 5-HT neurotransmission can alleviate depression in some patients.[118] Polymorphisms in the promotor region of the SERT gene have identified three variants of the allele described as homozygous long (l/l), homozygous short (s/s), and heterozygous (s/l) isoforms of the proteins. The l/l variant is associated with greater SERT function than the other two variants. Selective serotonin reuptake inhibitors (SSRIs, see the following) appear to be less effective in patients carrying the short (s/s) variant of the gene. Moreover, SERT polymorphisms appear to alter one's susceptibility to certain psychiatric disorders.[108]

Serotonin receptors

In the last 20 years, there has been an explosion of information about the 5-HT receptor. Using DNA cloning technology, four separate families of serotonin receptors with 15 distinct receptor subtypes have now been described. These include the 5-HT_1 subfamily (including 5-HT_{1A}, 5-HT_{1B}, 5-$HT_{1Dalpha}$, 5-HT_{1Dbeta}, 5-ht_{1E}, and 5-HT_{1F}), the 5-HT_2 subfamily (including 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C}), the 5-HT_3 subfamily (5-HT_{3A} and 5-HT_{3B}), and a family that includes the individual 5-HT_4, 5-ht_5, 5-HT_6, and 5-HT_7 receptors. The lowercase "ht" designation (e.g., 5-ht) is used for receptors in which no known function or signaling system has yet been established.[119,120]

The 5-HT_1 subfamily is negatively coupled to adenylate cyclase through a G_i protein similar to the $alpha_2$ adrenergic receptor and, when activated, produces a decrease in the adenylate cyclase activity. The 5-HT_2 subfamily is linked to phospholipase C and the phosphoinositide second messenger system through a G_q protein similar to the $alpha_1$ adrenergic receptor. The 5-HT_4, 5-HT_6, and 5-HT_7 are positively coupled with adenylate cyclase through a G_s protein similar to the beta adrenergic receptors.[119] The intracellular signaling system for the 5-ht_{1E} and 5-ht_5 receptors has not been determined. There are no clinically used drugs that act on the 5-HT_5, 5-HT_6, or 5-HT_7 receptors; however, we are likely to see such drugs in the future.

The 5-HT_3 family was originally identified in the periphery.[121] These receptors are unique among the monoamine receptors in that, instead of being G-protein linked receptors (GPCRs), they are ligand-gated ion channels similar to the nicotinic ACh receptor. The 5-HT_3 receptor is a nonselective cation channel that allows Na^+ and K^+ to enter the cell when 5-HT is bound to it. Thus, the 5-HT_3 receptor produces excitation when activated. Originally, the 5-HT_3 receptor was identified primarily by its affinity for specific agonists and antagonists,[121,122] but it has now been cloned.[39] Indeed, at least two subtypes of 5-HT_3 receptors have now been identified (known as 3A and 3B), and there may be others. These subtypes differ in the protein subunit composition, much like the nicotinic ACh receptor or the $GABA_A$ receptor.[123] The 5-HT_3 receptors are present in the area postrema and autonomic afferent nerves where they play a role in promoting nausea and vomiting. Indeed, the 5-HT_3 antagonists *ondansetron* (Zofran®), *granisetron* (Kytril®), and *dolasetron* (Anzetmet®) are widely used to treat the nausea and vomiting associated with cancer chemotherapy. Another 5-HT_3 antagonist, *Alosetron* (Lotronex®), has been approved for the treatment of diarrhea associated with irritable bowel syndrome.[109] It is likely that, in the future, we will see 5-HT_3 antagonists used in the treatment of psychiatric disorders as drugs that are more selective for subtypes of the receptor become available.

Clinically useful drugs that alter serotonergic neurotransmission

FACILITATORS OF SEROTONERGIC NEUROTRANSMISSION

Drugs that increase the synthesis and/or release of 5-HT

Because the rate-limiting enzyme TPH2 is not saturated with tryptophan, it is possible to increase the synthesis of 5-HT by administering tryptophan. However, a number of factors affect the amount of tryptophan that actually gets into the brain, such as the ratio of tryptophan to other neutral amino acids in the plasma that compete with tryptophan for transport into the brain and the concentration of free fatty acids in the plasma, which compete with tryptophan for binding to plasma proteins.

Tryptophan administration has apparently been used in the treatment of depression, but its effectiveness has been questioned. It is also possible to increase the release of 5-HT from nerve terminals with *fenfluramine*, a drug that was marketed as an appetite suppressant (anorexiant) to treat obesity. Fenfluramine is no longer on the market in the United States because of toxicities associated with pulmonary hypertension and damaged heart valves. It was one of the ingredients in Fen–Phen used to treat obesity.

Drugs that are 5-HT agonists

The availability of agonists highly selective for specific subtypes of 5-HT receptors is low. Serotonin itself does not cross the blood–brain barrier, and many of the other agonists are hallucinogenic. However, there are three partial agonists for 5-HT_{1A} receptors (*ipsapirone*, *gepirone*, and *buspirone*) that are being used for the treatment of anxiety. Of these, buspirone (Buspar®) is the only one approved for use in the United States in the treatment of anxiety. *Sumatriptan* (Imitrex®), *zolmitriptan* (Zomig®), *naratriptan* (Amerge®), *almotriptan* (Axert®), *eletriptan* (Relpax®), *frovatriptan* (Frova®) and *rizatriptan* (Maxalt®) are agonists for the 5-HT_{1D} and 5-HT_{1B} receptors and are used widely for the treatment of migraine headache. The latter are believed

to act by increasing cerebral vascular constriction during the vasodilatory phase of a migraine headache.[124,125] They also reduce the release of inflammatory mediators from the nociceptive trigeminal nerve terminals innervating the dura matter that are believed to play a role in migraine headache.[126]

Drugs that block the reuptake or prevent enzymatic degradation of 5-HT

It is clear that the most common way to increase serotonergic neurotransmission, clinically, is to use a reuptake blocker (i.e., selective serotonin reuptake inhibitor or *SSRI*). The SSRIs approved for the treatment of depression include *fluoxetine* (Prozac®), *sertraline* (Zoloft®), *paroxetine* (Paxil®), *citalopram* (Celexa®), and *escitalopram* (Lexapro®). *Fluvoxamine* (Luvox®) and *clomipramine* (Anafranil®) are also SSRIs and are approved for the treatment of obsessive-compulsive disorder but not depression. In addition to their use in depression and obsessive-compulsive disorder, the 5-HT reuptake inhibitors can be used to suppress anxiety, and several are approved for this purpose. There is much speculation, with some supporting evidence, that the antidepressant and anxiolytic effects of SSRIs and 5-HT agonists (e.g., buspirone) are mediated by enhanced 5-HT neurotransmission via the 5-HT_{1A} receptors in specific brain regions (e.g., hippocampus, frontal cortex) while simultaneously reducing 5-HT neurotransmission via 5-HT_{1A} receptors in other brain regions (e.g., dorsal raphe nucleus).[108]

Monoamine oxidase inhibitors, described previously under norepinephrine, can also be used to enhance serotonergic neurotransmission because they will prevent the degradation of this amine as well.[1] However, the MAO inhibitors are not selective and could result in multiple effects due to an increase in the synaptic content of NE, dopamine, and 5-HT.

Drugs with mixed monoaminergic action

Several drugs that selectively inhibit the reuptake (inactivation) of both 5-HT and NE have been marketed for the treatment of depression. These drugs are referred to as serotonin and norepinephrine reuptake inhibitors (SNRIs). The SNRIs currently available for the treatment of depression include *venlafaxine* (Effexor), *desvenlafaxine* (Pristiq), *duloxetine* (Cymbalta), *milnacipran* (Savella used for fibromyalgia), and *levomilnacipran* (Fetzima, approved for depression).

Vortioxetine (Brintellix) is a drug with multiple actions on the serotonergic synapse that has been approved recently (2013) for the treatment of major depressive disorder. Vortioxetine has been referred to as a serotonin modulator and a serotonin stimulator. Its actions include inhibition of SERT (like the SSRIs), partial agonist activity at the 5-HT_{1A} and 5-HT_{1B} receptors, and antagonist activity at the 5-HT_{1D}, 5-HT_7, and 5-HT_3 receptors. There is also some evidence that vortioxetine can inhibit NE reuptake, giving it some SNRI activity. Whether effects other than its inhibition of SERT and NET contribute to the antidepressant action of vortioxetine remains to be determined.[127]

INHIBITORS OF SEROTONERGIC NEUROTRANSMISSION

There are few drugs clinically available that reduce serotonergic neurotransmission, and these fall into one of two categories: 1) drugs that interfere with storage of 5-HT and 2) drugs that block 5-HT receptors. The drugs that interfere with the storage of 5-HT are the same drugs that do this to NE and dopamine—namely, reserpine or tetrabenazine. The only one used clinically is reserpine, which is used to treat hypertension (discussed under norepinephrine). A side effect of reserpine is depression with suicidal tendency, which apparently results from the depletion of brain NE and 5-HT.

There are a whole host of experimental drugs that block 5-HT receptors, but only a few are available for clinical use at the present time. These include *methysergide* (Sansert®), a nonselective (broad spectrum) 5-HT antagonist, which was used to prevent the onset of migraine headaches (approval removed in the United States), and selective 5-HT_3 antagonists ondansetron (Zofran®) and granisetron (Kytril®), which are used to treat nausea and vomiting along with the other 5-HT_3 antagonists described previously (see "Serotonin receptors"). Given the multitude of 5-HT receptors that have been described in recent years, it is clear that the drug companies have many new drug targets. Although there are few selective antagonists for 5-HT receptors currently available, it is hoped that selective 5-HT antagonists will become available in the near future.

Serotonin has been implicated in a wide variety of functions, including anxiety, sleep states, pain perception, affective states (depression), food intake, thermoregulation, seizures, vomiting, neuroendocrine functions, and blood pressure. New drugs to treat disorders of these functions may well come from selective agents for modifying serotonergic neurotransmission.

Serotonergic drugs in the TBI patient

The role of 5-HT in brain injury and the recovery of function after injury is not clear. Studies done in animal models of TBI suggest that acute synthesis of 5-HT increases after TBI and that this is associated with a decrease in local cerebral glucose utilization in the cerebral cortex.[128] Additionally, inhibition of 5-HT synthesis with *p*-chlorophenylalanine was found to reduce cerebral blood flow changes, cerebral edema, and cell injury following TBI in animals.[129] Such findings suggest that acute elevation of 5-HT may contribute to the damage after TBI. However, several other studies show that drugs that mimic the action of or increase the concentration of 5-HT at its receptors in the brain enhance the recovery of function after TBI. For example, some experimental agonists (i.e., repinotan and 8-OH-DPAT) as well as an approved agonist (buspirone) for the 5-HT_{1A} receptor have been shown to improve learning

deficits in rats following TBI.[130,131] The SSRI antidepressant fluoxetine has also been shown to facilitate cognitive function in rats following TBI.[132] Fluoxetine has also been found to reduce OCD in TBI patients.[133] The antidepressant effects of SSRIs are also seen in TBI patients, just as they are in the noninjured population. Thus, it would appear that enhancing serotonergic neurotransmission is beneficial in TBI patients. However, more studies are needed before definitive conclusions can be reached regarding the use of serotonergic drugs for TBI patients. There is evidence that 5-HT enhances the expression of brain-derived neurotrophic factor (BDNF) and that BDNF promotes the growth of 5-HT neurons. These two signaling molecules seem to interact to enhance neuronal plasticity and prevent neurodegeneration.[134] Thus, 5-HT may facilitate recovery of brain function after injury via increasing BDNF. There is evidence that this may also play a role in the antidepressant effects of SSRIs.

GAMMA AMINOBUTYRIC ACID (GABA)

GABA is one of two amino acids (the other being glycine) that function as major inhibitory neurotransmitters in the mammalian CNS. GABA is present in essentially all areas of the CNS and has been implicated in the mechanism of action of several antiepileptic drugs as well as in the action of hypnotics (sleeping aids), anesthetics, and antianxiety drugs. The concentration of GABA in the brain is much higher than that of the monoamine neurotransmitters. Studying the neurotransmitter role of GABA and other amino acids has not been easy for researchers because these amino acids also play a metabolic role and are structural components of proteins. Thus, within the neuron, there is both a metabolic and a neurotransmitter pool of GABA. Determining whether one is dealing with the metabolic pool or the neurotransmitter pool of GABA is crucial but not always easy.

GABAergic neurons are widely distributed throughout the brain and spinal cord. In most areas of the brain, GABAergic neurons are short interneurons (inhibitory interneurons) rather than long projection cells. However, some GABAergic pathways have been mapped, and these include the pathway from the striatum (caudate) to the substantia nigra and another from the globus pallidus to the subthalamic nucleus. The purkinje cells of the cerebellum are also GABAergic, and some project to the lateral vestibular nucleus in the medulla oblongata.[135]

Synthesis, storage, release, and inactivation of GABA

GABA is synthesized from glutamic acid by the enzyme glutamic acid decarboxylase (GAD).[136] The glutamate is formed from glucose via the glycolytic pathway and the Krebs cycle.[136,137] Pyruvate, formed from glucose, enters the Krebs cycle as acetyl CoA and is converted to alpha ketoglutarate, the first component of the "GABA shunt," which leads to the synthesis of GABA (Figure 16.10).[137]

The GABA shunt represents an alternative pathway between two intermediates of the Krebs cycle. In this shunt, alpha ketoglutarate is converted to glutamic acid in a transamination reaction involving GABA-alpha ketoglutarate transaminase (GABA-T). The glutamate is then converted

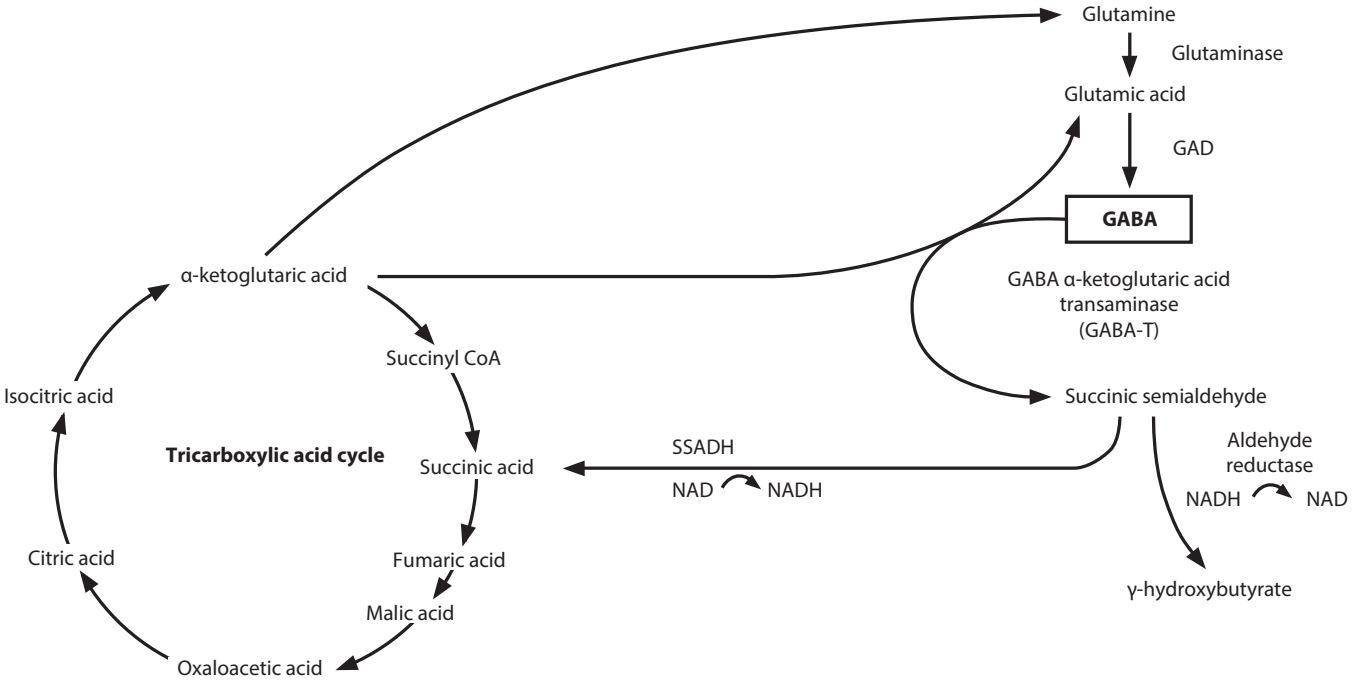

Figure 16.10 Synthesis and degradation of GABA via the GABA "shunt" of the tricarboxylic acid (Krebs) cycle. Note that glutamate is a precursor of GABA.

to GABA by the enzyme GAD. Because GAD is only expressed in cells that use GABA as a neurotransmitter, it has served as a cell marker for mapping GABAergic neurons in the CNS.[136]

GABA is degraded by GABA-T (the enzyme that converts α-ketoglutarate to glutamate), which converts it to succinic semialdehyde. In this process, a molecule of GABA can be broken down only if a molecule of precursor (glutamate) is formed (Figure 16.10).[136] The succinic semialdehyde is then converted to succinic acid by the enzyme succinic semialdehyde dehydrogenase (SSADH), returning the shunt to the Krebs cycle (Figure 16.10).

GABA released from neurons may also enter the glutamine loop. In the latter case, the GABA is taken up by glial cells in which it is metabolized by GABA-T to succinic semialdehyde while generating glutamate in the same reaction (see above). The glia cannot convert glutamate to GABA because they lack GAD, but they convert the glutamate to glutamine with glutamine synthetase. The newly formed glutamine is then transported out of the glial cells and into the GABAergic nerve endings where it can be converted back to glutamate by the enzyme glutaminase. This provides another mechanism by which neurons can recycle GABA.[136] Note that the GABA transporter (discussed in the following) in glial cells enabling the uptake of GABA provides one of the ways in which synaptic cleft GABA is inactivated.

GAD and GABA-T can be manipulated pharmacologically. Both enzymes require pyridoxal phosphate (vitamin B_6) as a cofactor, but the subcellular location of the enzymes differs for the two. GAD is a soluble enzyme found in cytoplasm and GABA-T that is a mitochondrial enzyme.

It turns out that there are two types of GAD, each of which is formed from a different gene. The two types of GAD are referred to as GAD_{65} and GAD_{67}.[39,138] These forms differ in molecular weight, amino acid sequence, interaction with pyridoxal phosphate, and expression in different parts of the brain.[1] GAD_{65} appears to be localized to nerve terminals to a greater extent than GAD_{67} and seems to be involved in the synthesis of GABA that is packaged in synaptic vesicles, and GAD_{67} appears to be associated with the synthesis of nonvesicular GABA.[136] The significance of this is not clear. Of interest is the finding that GAD is the target of antibodies present in people who later develop insulin-dependent diabetes mellitus (Type 1 diabetes). In these patients, the antibody that destroys the beta islet cells of the pancreas is directed at GAD.[139,140]

GABA-T is also a pyridoxal phosphate-dependent enzyme that has been purified to homogeneity and was shown to have a molecular weight of about 109,000. The availability of alpha ketoglutarate may regulate the tissue levels of GABA. Variations in the concentration of alpha ketoglutarate could be responsible for the postmortem increase in GABA levels that are known to occur. For example, when respiration stops, the dependence of the Krebs cycle on respiration results in a marked decline in the availability of alpha ketoglutarate and the consequent reduction in GABA-T activity, which depends on alpha ketoglutarate for transamination. However, even with anoxia, GABA synthesis can still occur from glutamate via GAD, which is an anaerobic enzyme.[136]

GABA and other amino acid neurotransmitters are stored in and released from synaptic vesicles via exocytosis. However, both a vesicular and a cytoplasmic pool of GABA exist within the neuron and release occurs in both a Ca^{2+}-dependent and Ca^{2+}-independent manner.[141] Thus, a nonvesicular release of GABA has been found (see the following).[1,141] The cytoplasmic release may involve an exchange transporter between cytoplasmic and extracellular compartments. The latter exchange system seems to be coupled to a Na^+ transporter.[141]

As has been demonstrated for the uptake of NE and 5-HT into synaptic vesicles, GABA may be taken up into synaptic vesicles by a Na^+-independent transporter that is driven by a proton gradient maintained by a Mg^{++}-ATPase.[142] The transporter that loads GABA into synaptic vesicles is referred to as the vesicular GABA transporter (VGAT). Because this is the same transporter that loads glycine into synaptic vesicles, it has also been referred to as the vesicular inhibitory amino acid transporter (VIAAT).[58]

Following release from nerve endings, high-affinity uptake by neurons and glial cells is believed to be responsible for terminating the neurotransmitter action of GABA.[136] The plasma membrane transporter responsible for GABA uptake requires extracellular sodium and chloride ions. Two sodiums and one chloride ion are cotransported with each molecule of GABA.[39,143,144] The high-affinity uptake transporter of GABA is capable of moving GABA against a concentration gradient and, generally, concentrates the amino acid three to four orders of magnitude higher in the intracellular compartment than in the extracellular compartment.[136]

High-affinity uptake of GABA and excitant amino acids into neurons and glial cells has also been demonstrated by several laboratories.[145] The operation of the glial transporter is similar to the neuronal transporter and is in the direction of net uptake. Four distinct plasma membrane GABA transporters have been cloned. These are referred to as *GAT-1*, *GAT-2*, *GAT-3*, and *BGT-1*.[58,146] Such findings suggest a much greater heterogeneity of GABA transporters than was expected, and the significance of this heterogeneity is still unknown. Although it was hoped that these could be localized to either neurons or glia, only GAT-3 was localized to glia, and GAT-1 and GAT-2 were found to be expressed in both neurons and glia.[58] However, some regions of the brain appear to contain a predominance of one type of transporter over another.[146] Of interest is the finding that certain drugs (e.g., tiagabine) appear to preferentially inhibit GAT-1.[58] New drugs with selective effects on specific transporters are likely to be developed in the future and some may have therapeutic benefit in TBI patients.

GABA receptors

Two subtypes of GABA receptor have been described in detail and are referred to as $GABA_A$ and $GABA_B$ receptors.

The $GABA_A$ receptor has been more thoroughly investigated and is a ligand-gated ion channel that functions as a channel for the chloride ion.[136,147,148] This receptor is usually placed in a gene superfamily that also includes the nicotinic acetylcholine receptor, $5\text{-}HT_3$ receptor, and the glycine receptor. This gene superfamily is sometimes called the *cys-loop family*, which distinguishes it from the excitatory amino acid ligand-gated channel family of receptors.[136] $GABA_A$ receptors are stimulated by GABA, *muscimol*, and *isoguvacine* and are blocked by the convulsants *bicuculline* (competitive antagonist) and *picrotoxin* (noncompetitive antagonist). The $GABA_A$ receptor is a heteropentamer composed of five polypeptide subunits forming the chloride ion channel in the cell membrane. The $GABA_A$ receptor contains several distinct binding sites for different chemicals that can modulate its function (see the following).

Molecular cloning has indicated that there are 19 different but closely related polypeptide subunits, any five of which (in combination) can form a $GABA_A$ receptor. These include six different alpha, four beta, three gamma, one delta, one epsilon, one theta, one pi, and three rho subunits.[1,136] Like the nicotinic ACh receptor, each subunit has four membrane-spanning regions, one of which is believed to contribute to the walls of the ion channel. Scientists often use cells that do not normally express (contain) $GABA_A$ receptors, such as the Xenopus oocyte, to study the molecular characteristics of these receptors. Adding the genes for the $GABA_A$ receptor to these cells causes them to express $GABA_A$ receptors, the function of which can then be studied. By examining recombinant receptors in Xenopus oocytes, it is also possible to determine the importance of each subunit. It appears that $GABA_A$-regulated chloride conductance, which is inhibited by bicuculline and picrotoxin, can be obtained with the expression of alpha and beta subunits only. However, benzodiazepine (discussed in the following) sensitivity is only obtained if the neurons contain the alpha, beta, and the $gamma_2$ subunits.[136,149] Thus, recombinant receptors containing α, β, and γ_2 subunits most closely resemble $GABA_A$ receptors found in the brain, and the specific subtype of α and β subunits present determines the various affinities for drugs, such as benzodiazepines. The resulting heteropentameric chloride channel must contain at least two α and two β subunits, and as was true of the nicotinic ACh receptor, it takes two molecules of GABA to open the channel. The GABA binding sites are at the interface of an α and β subunit. The GABA-gated chloride channel also contains binding sites for other ligands (drugs) that allosterically modulate (positively or negatively) the channel. These include a binding site for benzodiazepines, barbiturates, intravenous anesthetics (e.g., *propofol*), anesthetic steroids, and ethanol. Benzodiazepines bind to the interface of an α and γ subunit.[136]

The $GABA_B$ receptor is insensitive to bicuculline, 3-aminopropanesulfonic acid, and isoguvacine, but it has a weak sensitivity to muscimol and is stereospecifically sensitive to *baclofen* (Lioresal®). The $GABA_B$ receptor, unlike the $GABA_A$ receptor, is a GPCR linked to a second messenger system, such as the muscarinic cholinergic and the noradrenergic receptors. Thus, $GABA_B$ receptors are seven transmembrane proteins. However, it has recently been found that there are two subunits of this receptor (R1 and R2), and to be functional, they seem to form a dimer (two proteins can form a dimer) or heterodimer of R1 and R2 subunits.[136] Most of the early studies suggest that $GABA_B$ receptors are primarily presynaptic receptors involved in inhibiting the release of other neurotransmitters; however, it is now clear that they may also mediate postsynaptic inhibition as well.[150,151] Basically, two membrane effects have been attributed to the $GABA_B$ receptors, both of which lead to neuronal inhibition: 1) a decrease in Ca^{2+} conductance (usually a presynaptic effect leading to decreased neurotransmitter release) or 2) an increase in K^+ conductance (leading to postsynaptic hyperpolarization) as occurs in hippocampal pyramidal cells following the application of a $GABA_B$ agonist. It has been suggested that the reason for the different effects may be related to the fact that $GABA_B$ receptors are linked to different channels in different locations. Thus, they are probably linked via second messengers to Ca^{2+} channels on presynaptic terminals and to K^+ channels at postsynaptic sites.[151] The second messengers to which $GABA_B$ receptors have been suggested to be linked are cAMP (decreased) and (by mechanisms still under investigation) the phosphatidyl inositols.

The classical agonist for $GABA_B$ receptors is baclofen. A number of studies have been carried out with baclofen to assess the function of $GABA_B$ receptors. However, one difficulty with the use of baclofen is that it crosses the blood–brain barrier rather poorly.[151]

A third subtype of GABA receptor called the $GABA_C$ receptor has also been identified on the basis of its lack of sensitivity to bicuculline and baclofen and its sensitivity to *cis*-4-aminocrotonic acid (agonist). These receptors were first discovered in the retina, but they have also been found in the cerebellum, optic tectum (superior colliculus), hippocampus, and spinal cord. $GABA_C$ receptors form a chloride channel from five rho subunits and are, therefore, referred to as *homomeric channels*.[39,152] Although many known drugs and chemicals act on $GABA_A$ and $GABA_B$ receptors, we have no pharmacological agents selective for the $GABA_C$ receptor.

Clinically useful drugs that alter GABAergic neurotransmission

FACILITATORS OF GABAERGIC NEUROTRANSMISSION

GABA agonists

Several experimental drugs are used as agonists to study the GABA binding site on the $GABA_A$ receptor, including *muscimol*, *THIP*, and *isoguvacine*. In fact, there are no clinically approved drugs that act as $GABA_A$ agonists per se. However, as previously mentioned, the $GABA_A$ receptor has several different binding sites in addition to those for

GABA. The *benzodiazepines* are allosteric modulators of the $GABA_A$ receptor, which, when bound to their high-affinity site on the $GABA_A$ receptor, enhance the binding of GABA to its binding site and increase the frequency of chloride channel opening.[136] The benzodiazepines are, by far, the most popular clinically used drugs whose mechanism of action involves the $GABA_A$ receptor. The latter compounds have a wide variety of uses, including the treatment of anxiety, seizures, insomnia, and muscle spasms, all or any of which may occur following TBI. The benzodiazepines bind with high affinity to a site on the chloride channel and enhance the inhibitory action of GABA, and they are therefore prescribed for the aforementioned conditions.

Benzodiazepines used to treat anxiety include *diazepam* (Valium®), *oxazepam* (Serax®), *alprazolam* (Xanax®), and *lorazepam* (Ativan®). Those used as antiepileptic drugs include diazepam, *clonazepam* (Klonopin®), and *clorazepate* (Tranxene). Benzodiazepines used as hypnotics include *flurazepam* (Dalmane®), *temazepam* (Restoril®), *triazolam* (Halcion®), and *quazepam* (Doral®). There are now several novel benzodiazepine receptor agonists, which, chemically, are not benzodiazepines, but which bind to the same binding site as benzodiazepines on the GABA/chloride channel.[153] These novel agents are now widely used as hypnotic drugs (sleeping pills) to treat insomnia and include *zolpiden* (Ambien®), *zaleplon* (Sonata®), and *eszopiclone* (Lunesta®). These are sometimes referred to as Z compounds. Additionally, all of these drugs have muscle relaxant properties, but diazepam is, probably, most commonly used for this purpose, and the Z compounds are less effective as muscle relaxants.[154]

There is another major class of drugs that act as positive allosteric modulators of the $GABA_A$ chloride channel. These are the barbiturates, such as *phenobarbital*, *pentobarbital*, and *secobarbital*. The barbiturates are also widely used as hypnotic agents (sleeping pills) and as adjuncts to anesthetics during surgery. Moreover, some barbiturates find important use as antiepileptic drugs (e.g., phenobarbital and *primidone* [Mysoline®]). Importantly, barbiturates bind to a different site on the chloride channel than do the benzodiazepines, and they increase the duration of chloride channel open time (prolonging inhibition) rather than the frequency of channel opening.

$GABA_B$ receptors also mediate inhibition in the nervous system through the action of G-proteins and second messengers. *Baclofen* (Lioresal®) is a $GABA_B$ receptor agonist that has long been used to treat spasticity in patients with multiple sclerosis or other neurological diseases.

Drugs that inhibit GABA reuptake

Because the major mechanism for terminating the action of GABA following its release from nerve endings is reuptake into GABAergic neurons and glial cells, drugs that block this process will enhance and prolong the action of released GABA, just as the SSRIs do for 5-HT. Currently, *tiagabine* (Gabitril®) is the only GABA reuptake inhibitor available for clinical use. Tiagabine blocks the uptake of GABA in both neurons and glial cells via its selective blockade of GAT-1 rather than GAT-2 or GAT-3. This effectively prolongs the inhibitory action of synaptic GABA. Tiagabine is an antiepileptic drug used for the adjunctive treatment of complex partial seizures.

Drugs that block GABA degradation

There are a whole host of compounds used experimentally to block GABA-T, but only one of these is used clinically, and that is gamma vinyl-GABA or *vigabatrin* (Sabril®), which is used as an antiepileptic in Europe and is approved with "restricted access" in the United States for the treatment of refractory complex partial seizures and infantile spasms.[155,156] Vigabatrin is an irreversible GABA transaminase inhibitor that has been shown to be of value in some drug-refractory epileptic patients. *Valproic acid* (Depakene®) has also been shown to elevate brain GABA levels by inhibiting GABA-T.[157] Valproic acid is used to treat a variety of seizure types including absence and generalized tonic-clonic. Whether the action of valproic acid in epilepsy is due primarily to an enhancement of the action of GABA is not known because it has another important effect that is probably responsible for its effect in tonic-clonic seizures; namely, it blocks sodium channels in a frequency- and voltage-dependent fashion.[155]

INHIBITORS OF GABAERGIC NEUROTRANSMISSION

Drugs that block GABA receptors

There are several GABA antagonists available for experimental use. However, because all the $GABA_A$ antagonists are convulsants, they have no clinical use at the present time. The classical $GABA_A$ antagonist is bicuculline, but picrotoxin is also an antagonist. *Saclofen* and *phaclofen* are $GABA_B$ antagonists that are being used in experimental animals to help deduce the functional importance of the $GABA_B$ receptor. There are also a group of experimental compounds that bind to the benzodiazepine binding site on the chloride channel and cause a reduction in the effectiveness of GABA. The latter compounds, of which *beta-carboline-3-carboxylic acid* (and other beta carbolines) is an example, are called *inverse agonists*. Clearly, the GABA antagonists and the inverse benzodiazepine agonists are proconvulsant and have no clinical use in medicine. However, it is possible that such drugs may be developed for use in the TBI patient (see the following). Of clinical importance is *flumazenil* (Romazicon®), a specific antagonist at the benzodiazepine binding site on the GABA receptor that is used to reverse the effects of benzodiazepines in the treatment of toxicity from overdose.[58]

GABAergic drugs in the TBI patient

GABA is the major inhibitory neurotransmitter in the brain, and therefore, changes in GABAergic neurotransmission can have major consequences. In general, anything that reduces GABA neurotransmission can cause seizures

and would be detrimental to the patient. Indeed, loss of GABAergic neurons following TBI may be responsible for posttraumatic epilepsy. However, immediately following TBI in animals, it appears that GABA release is increased (as is the case for several other neurotransmitters).[158]

The increase in GABA release may represent a compensatory attempt to reduce seizures in the injured region. However, experimental TBI studies have found a decrease in benzodiazepine receptor binding, which may also reflect a reduction in GABA receptor function because the benzodiazepine binding site is on the same chloride channel as the GABA binding site.[159]

Drugs that facilitate GABAergic neurotransmission are widely used in TBI patients. For example, $GABA_B$ agonists, such as baclofen, are used to treat spasticity, and benzodiazepines, such as clonazepam and diazepam, are used to suppress seizures and anxiety. In general, however, drugs that facilitate neurotransmission at $GABA_A$ receptors (e.g., benzodiazepines, barbiturates, and some antiepileptics) may impair memory and cognition and could ultimately retard recovery of intellectual function in TBI patients.[160] Thus, it is not surprising to see that an inverse benzodiazepine agonist (MDL 26479, suritozole) that lacks proconvulsant or anxiogenic effects has been shown to reduce cognitive deficits in rats following TBI.[55]

GLYCINE

Glycine has the simplest chemical structure of any amino acid, and it is not an essential component of the diet. It is believed to function as a neurotransmitter primarily in spinal cord interneurons (e.g., Renshaw cell, which mediates recurrent inhibition) and in the brain stem.[1] Like GABAergic synapses, all of the glycinergic synapses appear to be inhibitory. This inhibition is mediated through a ligand-gated chloride channel, which, as indicated previously, places these receptors in a common family with the nicotinic ACh, $GABA_A$, and $5\text{-}HT_3$.

The anatomical distribution of glycinergic neurons has not been extensively mapped. However, the concentrations of glycine found in the spinal cord (dorsal and ventral horn), medulla, and pons are higher than in other CNS regions. Neuronal pathways suggested to be glycinergic include spinal interneurons, a corticohypothalamic pathway, reticulospinal projections from the raphe and reticular formation, brain stem afferents to the substantia nigra, cerebellar golgi cells, and retinal amacrine cells.[135,161]

Synthesis, storage, release, and inactivation of glycine

Glycine is synthesized from glucose via the glycolytic pathway to produce 3-phosphoglycerate and 3-phosphoserine, which forms serine. Serine (the immediate precursor of glycine) is converted to glycine by the enzyme serine hydroxymethyltransferase (SHMT), which is found in the mitochondria. Radioactive tracer studies show that most of the glycine in the brain is made from serine.[162] SHMT requires tetrahydrofolate, pyridoxal phosphate, and manganese ion for activity.[136]

Glycine appears to be abundant in the CNS, and it is not clear what factors, if any, are rate limiting in the overall synthesis. Moreover, it is not clear whether neurons utilizing glycine as a neurotransmitter must synthesize it *de novo* or whether they accumulate existing glycine.[1] SHMT is inhibited by pyridoxal phosphate inhibitors, which also interfere with GABA synthesis and degradation. Enzymatic degradation of glycine can occur via a glycine cleavage system, which is also located in the mitochondria, mainly of astrocytes.[136] Genetic mutations in the proteins of the glycine cleavage system can cause metabolic disorders known as *nonketotic hyperglycinemias*.[39]

Glycine is packaged into vesicles from which it is released. The evidence suggests that glycine uptake into the vesicle (like that of GABA and glutamate) is driven by an electrochemical proton gradient generated by an ATP-dependent proton pump (ATPase) located in the synaptic vesicle membrane. Kish et al.[163] have found that the glycine vesicle transporter has a different substrate specificity from that of the GABA uptake system and a different regional distribution in the brain, suggesting they are in separate neurons. The likelihood that there are both vesicular and cytoplasmic release of glycine, as there appears to be for GABA, remains very high.

After its release into the synaptic cleft, glycine is primarily inactivated by reuptake into the terminal of the releasing neuron or by uptake into glial cells. Glycine reuptake is carried out by a glycine transporter in the membrane. The Na^+ and Cl^- electrochemical gradients assist in the movement of glycine against its concentration gradient.[161] Two glycine membrane transporters have been identified by molecular cloning: GLYT-1 and GLYT-2. It appears that GLYT-1 is found in both neurons and glial cells, and GLYT-2 is localized to neurons. Both transporters are expressed in the hindbrain whereas GLYT-1 can also be found in forebrain areas even though there are few, if any, glycinergic terminals. Because glycine also functions as a coagonist with glutamate at NMDA receptors (see text on glycine receptors and EAA), there is speculation that the GLYT-1 transporter might regulate glutamate receptor function in forebrain areas.[161] Selective inhibitors of the glycine transporter are not yet available but could become useful drugs in the future for the treatment of pain or epilepsy (see the following). It has been suggested that GLYT-1 is the primary glial transporter, and GLYT-2 is the primary neuronal transporter, but this remains somewhat controversial.[1]

Glycine receptors

As indicated previously, the glycine receptor is a member of a super family of ligand-gated ion channels for which the ligand binding site and the ion channel are in the same molecule. In this regard, the glycine receptor, like that of the nicotinic ACh and $GABA_A$ receptors, has been classified as

an ionotropic receptor.[135] The glycine receptor, which consists of five subunits forming a chloride channel (i.e., is a pentamer), has been cloned.[164] Two polypeptide subunits (α and β) have been shown to form a pentameric chloride ion channel.[136]

Like the nicotinic ACh and GABA receptors, the subunits of the glycine receptor have four hydrophobic membrane-spanning regions (M1–M4). Three alpha and two beta subunits are often responsible for forming the ion channel.[165]

The glycine receptor is associated with a 93 kD protein, called *gephyrin*, which associates with the intracellular domain of the beta subunit. Gephyrin is believed to function as an anchoring protein that connects the membrane receptor protein with the protein tubulin in the cytoplasm.

Strychnine is the classical glycine antagonist, and radioactive strychnine was originally used to map the distribution of glycine receptors in the CNS. The strychnine binding site is on the 48-kDa subunit, which is where glycine also binds.[165]

Glycine also has an action at a strychnine-insensitive receptor that has been linked to the NMDA excitatory amino acid receptor.[136] This is a high-affinity site that appears to increase the action of glutamate at its NMDA receptor.[166] The strychnine-insensitive glycine binding site has a widespread distribution in the brain, which corresponds to the distribution of the NMDA receptors. Thus, glycine, in submicromolar concentrations, appears to enhance the action of excitant amino acid neurotransmitter glutamate at the NMDA receptor (see the following) by functioning as a coagonist.[166] In this regard, it appears to be analogous to the interaction between the GABA receptor and the benzodiazepine binding site. The strychnine-insensitive glycine binding site (NMDA receptor) also appears to have an endogenous antagonist. The tryptophan metabolite, kynurenic acid, is an antagonist of the glycine-binding site on the NMDA receptor. However, 7-cholorkynurenic acid is a more selective and more potent antagonist and is now being widely used to study this glycine receptor.[166]

Clinically useful drugs that alter glycinergic neurotransmission

At the present time, there are no clinically available drugs whose mechanism of action is mediated through glycinergic neurotransmission. However, there is an experimental drug called *milacemide* that is believed to increase glycine levels in the brain and has been shown to have anticonvulsant effects in experimental animals. Glycinergic neurons in the brain stem and spinal cord have been shown to play a role in suppressing pain, and there is now much interest in developing inhibitors of the glycine transporter-2 (GlyT2) to treat chronic pain.[167] At the present time, we have no clinically useful antiepileptic drugs that act on glycine neurotransmission.[1]

As far as antagonists are concerned, strychnine, which is a convulsant drug, was once used to treat a variety of disorders as well as being a potent poison. This agent no longer finds any medical use. As indicated previously, glycine appears to also bind to a site on the NMDA receptor (the so-called *strychnine-insensitive* receptor) to enhance the excitatory effects of glutamate or aspartate. Thus, at this site, glycine is proconvulsant. At the present time, there is considerable interest among drug companies to explore the use of strychnine-insensitive glycine antagonists (e.g., 7-chlorokynurenic acid) as potential antiepileptic drugs, and it is conceivable that we will see such agents available in the future. The ability of glycine to enhance the excitatory effects of glutamate may stem from its ability to block NMDA receptor desensitization.[1] There is considerable interest in drugs that selectively activate this strychnine-insensitive glycine site on the NMDA receptor to enhance glutamate action as therapeutic agents for the treatment of schizophrenia (see following section on NMDA receptor).

Glycinergic drugs in the TBI patient

As indicated previously, there are no drugs currently available that modulate glycine neurotransmission. The antagonist at the strychnine-insensitive glycine receptor (7-chlorokynurenic acid) may prove to be useful in the future. At present, there is no information on whether or not glycinergic drugs would be useful in the TBI patient.

L-GLUTAMIC ACID

The major excitatory neurotransmitter in the CNS is glutamic acid or glutamate. Aspartate is also plentiful and was once thought to function as an excitatory amino acid neurotransmitter, but it is not concentrated in synaptic vesicles and therefore is unlikely to function as a neurotransmitter.[168] Glutamate is found in higher concentrations than any other free amino acid in the CNS, being three or four times higher than aspartate and six times higher than GABA.[168] The role of glutamate as an excitatory neurotransmitter continues to be the subject of intense investigation, in part, because of glutamate's abundance and importance in so many neural pathways and, in part, because of studies implicating it in such pathological conditions as epilepsy, schizophrenia, postanoxic cell loss, and neurotoxicity as well as in such normal functions as learning and memory.[168] It has been suggested that 80%–90% of the synapses in the mammalian brain use glutamate as a neurotransmitter. It has also been estimated that the repolarization of membranes depolarized by glutamate uses about 80% of the brain's energy expenditure.[168]

So glutamatergic neurons are found throughout the CNS. There are, however, some specific pathways that have been mapped using lesion and biochemical analyses. These include the well-known corticostriate pathway from the cerebral cortex to the striatum as well as many other corticofugal pathways.[135,168] In addition, the perforant pathway, from the entorhinal cortex to the dentate gyrus of the hippocampus, contains a heavy glutamatergic component as do

the mossy fibers from the dentate gyrus to the CA3 region and the Schaffer collaterals from CA3 to CA1 of the hippocampus.[135] The dorsal horn of the spinal cord has a high concentration of glutamate, which disappears after cutting the primary sensory afferents, indicating that glutamate is an important neurotransmitter of the primary sensory afferents. Although glutamate is also the immediate precursor of GABA in GABAergic neurons, the two neurotransmitters are typically stored and released from separate neurons and do not directly transmit signals from the same neuron. However, there is now evidence, in selected neuronal pathways, for neurons that store and release both GABA and glutamate. Of interest is a pathway from the basal ganglia to the lateral habenula (in the thalamus) containing neurons that use glutamate for excitation and GABA for inhibition, which appears to be important in regulating states of mood (e.g., depression).[169]

Synthesis, storage, release, and inactivation of glutamate

Glutamate is a nonessential amino acid (not needed in the diet) that does not cross the blood–brain barrier. Therefore, it must be synthesized in the brain.[135] Essentially, all the glutamate in the brain is derived from glucose via the tricarboxylic acid (TCA) cycle. Glucose is converted to α-ketoglutarate via the TCA cycle, which, in turn, is converted to glutamate by transamination (addition of an amino group). The glutamate formed from glucose, however, occurs in all brain cells (neurons and glia) and has many roles in the brain. For example, in addition to its neurotransmitter role, it is an important component of protein and peptide (e.g., glutathione) synthesis.[170] It also functions as an amino group acceptor to detoxify ammonia in the brain, and it is the immediate precursor of GABA for GABA synthesis in GABAergic neurons. In neurons, therefore, there are two pools of glutamate, one of which is used for neurotransmission and the other as a metabolic precursor.[168]

Within glutamatergic neurons, the transmitter pool of glutamate is synthesized from either glucose or glutamine. Although both glucose (via α-*ketoglutarate*) and glutamine are readily converted to glutamate, the pool derived from glutamine is preferentially released,[162] suggesting that this may be more important. However, *in vivo* studies using ^{14}C-glucose and ^{14}C-glutamine showed that released glutamate was derived equally from glucose and glutamine.[171]

The two main routes of synthesis are shown in Figure 16.11. Glial cells play a role in terminating the action of glutamate and in its synthesis.[172] The latter cells actively accumulate glutamate by a sodium-dependent membrane transporter after its release and convert the glutamate to glutamine by the enzyme glutamine synthetase. The glutamine can be transported out of glial cells and into glutamatergic neurons where it is converted back to glutamate by the enzyme glutaminase (in the mitochondria).[168] This appears to be one of the mechanisms by which the neurotransmitter is recycled. The other mechanism terminating the action of glutamate and recycling it is transport back into the neuron from which it was released (see the following).

After glutamate is synthesized in the neuron, it is transported into the synaptic vesicles via a transporter. The vesicular glutamate transporter protein is apparently the same transporter that moves inorganic phosphate ions across the cell membrane, but the one found in synaptic vesicles of glutamatergic neurons has been called *VGLUT*.[173] Three subtypes of VGLUT are expressed in the brain (VGLUT1–3).[168] Glutamate is released from neurons in a calcium-dependent manner by exocytosis.[58,168] Zinc is colocalized with glutamate in a subpopulation of synaptic vesicles in the brain and is released together with glutamate, allowing it to have a modulatory effect on some glutamate receptors.[168]

High-affinity uptake across the cell membrane is responsible for terminating the synaptic actions of glutamate. This uptake across the cell membrane is mediated by a sodium-dependent, high-affinity transporter that has been studied in synaptosomes and brain slices. It does not distinguish between L-glutamate, L-aspartate, and D-aspartate.[170,174,175] This transporter, referred to as the excitatory amino acid transporter (EAAT), is present in both neurons and glial cells and has an uneven brain regional distribution consistent with a role in neurotransmission. Five subtypes of EAAT have been identified, some of which have a distinct anatomical distribution in the brain and a specific sensitivity to pharmacological agents.[1] Both the neuronal and glial EAATs are believed to play an important role in terminating the action of glutamate following its release from nerve endings as was discussed previously for GABA. It is of interest that some glial cells also possess receptors for glutamate, which, when activated, lead to a transient increase in intracellular calcium (i.e., a Ca^{2+} wave) and which may pass from one glial cell to another and function as a form of intercellular communication.[176] Molecular cloning studies have been used to study the different EAATs.[58] These EAATs can

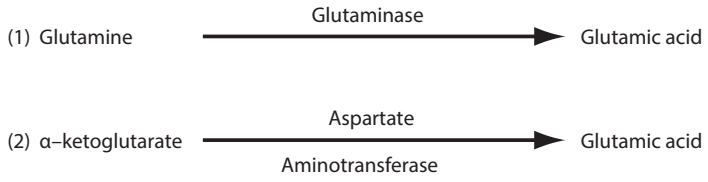

Figure 16.11 Two pathways that can synthesize glutamic acid in the brain. The glutamine and α-ketoglutarate (from glucose) pathways are primarily responsible for synthesizing glutamate in nerve terminals.

transport glutamate as well as aspartate in a high-affinity sodium-dependent manner. They are believed to be responsible for the majority of the glutamate inactivation in the CNS.[58] All five EAATs (EAAT1–EAAT5) have been cloned and studied in some detail. EAAT1 is expressed mainly in glial cells of the cerebellum whereas EAAT2 is expressed in astrocytes throughout the brain and EAAT3 is the main neuronal transporter throughout the brain.[1,58,168] EAAT4 is found primarily in Purkinje cells of the cerebellum, and EAAT5 is found in several types of cells in the retina.[58]

Excitatory amino acid neurotransmitter receptors

The EAA receptors (i.e., receptors for glutamate and aspartate) have been actively investigated over the last 25 years and are still among the most vigorously targeted areas of research by drug companies seeking new compounds for epilepsy, stroke, psychiatric disorders, and degenerative brain disease (e.g., Alzheimer's disease) and memory loss.

As is the case with other neurotransmitter receptors, there are two major types of EAA receptors based on the type of signal transduction system they use to mediate their effects: 1) *ionotropic glutamate receptors* (i.e., ligand-gated channels) and 2) *metabotropic glutamate receptors* (i.e., GPCRs).

The ionotropic glutamate receptors are ion channels for sodium, potassium, and calcium similar to the nicotinic ACh receptor. These ligand-gated channels are opened by glutamate as well as various synthetic chemicals with a similar structure leading to excitation (depolarization) of the neuron on which they are found. *Three subtypes* of ionotropic glutamate receptors have been identified based on the chemicals that were highly effective in activating them: 1) *N*-methyl-*D*-aspartate or *NMDA receptor*, 2) α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid or *AMPA receptor*, and 3) kainic acid or *kainate receptor*. In the past, these receptors were separated into NMDA and non-NMDA because of the antagonists that blocked either the NMDA or non-NMDA (AMPA, kainate) receptors. Another difference between NMDA and non-NMDA receptors is their selectivity for ion conductance with NMDA channels able to conduct sodium and calcium and non-NMDA (AMPA, kainate) that typically depolarize the cell with a sodium current. Just as the nicotinic ACh and GABA receptors were composed of several protein subunits that form the ion channel, the EAA receptors are also composed of subunits. However, unlike the nicotinic ACh, GABA and glycine receptors, which were composed of five subunits (i.e., pentamers), the ionotropic glutamate receptors are composed of four protein subunits (i.e., tetramers). A variety of protein subunits that comprise the EAA receptors have been identified through molecular cloning. The subunits for the NMDA receptor are referred to as *GluN1*, *GluN2A*, *GluN2B*, *GluN2C*, *GluN2D*, *GluN3A*, and *GluN3B*, and those for the AMPA receptor are designated as *GluA1–GluA4*. The protein subunits that form the kainate receptor include GluK1–GluK5.[168] The subunit composition of an NMDA or non-NMDA receptor may differ in different regions of the brain.

Of the ligand-gated EAA receptor channels, the NMDA receptor is unique in that it is 1) voltage–dependent as well as 2) ligand (agonist)-dependent. This means that it requires some depolarization of the membrane (i.e., voltage change) as well as agonist (glutamate) binding in order to open the channel. The depolarization is necessary to remove an Mg^{++} block within the ion channel.[168] The NMDA receptor also differs from the AMPA receptor by having at least six discrete binding domains for other ligands that modulate its function, which make it similar to the $GABA_A$-benzodiazepine receptor complex.[168] One of these binding sites is selective for glycine or a structurally related amino acid (e.g., D-serine), which must be present (bound) in order for glutamate to open the channel. In this regard, glycine is now referred to as a coagonist for the NMDA ionotropic glutamate receptor.[59,168,177] The glycine binding site on the GluN1 subunit of the NMDA receptor is sometimes referred to as a *strychnine-insensitive* glycine binding site (see previous section on Glycine receptors) because of its distinction from the inhibitory glycine receptor at other sites. There are some selective antagonists for this glycine site (e.g., 7-chlorokynurinate and 5, 7-dichlorokynurenic acid). As indicated previously, the NMDA receptor is also unique in that it conducts calcium as well as sodium into the cell.

The glutamate binding site on the NMDA receptor has several selective competitive antagonists (e.g., 2-amino-5-phosphonovalerate or *AP5*, 2-amino-7-heptanoate or *AP7*, and 2-carboxypiperazin propyl-1-phosphonic acid or *CPP*), which are available only as experimental drugs. In addition, some noncompetitive antagonists of the NMDA receptor have been discovered. These apparently bind to a site within the ion channel to inhibit neurotransmission. The latter compounds include such drugs as *phencyclidine* (PCP), *ketamine* (Ketalar®), and the experimental compound *MK-801* (dizocilpine).[39,168] The ionotropic glutamate receptors (especially the NMDA receptor) are believed to play an important role in synaptic plasticity, two forms of which are long-term potentiation (LTP) and long-term depression (LTD). Both LTP and LTD are believed to play important roles in learning and memory (see chapter in this text by Lehr).[168] Indeed, the NMDA receptor may be the primary receptor responsible for LTP. The distribution of the NMDA and non-NMDA glutamate (AMPA and kainate) receptors has been extensively mapped in the rat brain using radioactive ligands and autoradiography.[168]

Despite the important or critical role of glutamate as an excitatory neurotransmitter in the CNS in numerous pathways and its essential role in such important functions as learning and memory, it is like a double-edged sword. Excessive amounts of glutamate and other EAAs in the extracellular fluid of the brain have been shown to produce excitotoxicity (neuronal death) and/or seizures. These neurotoxic effects of excessive glutamate are also mediated through the ionotropic glutamate receptors, especially

those that increase the influx of calcium into the neuron (e.g., NMDA), but it is clear that activation of kainate and AMPA receptors also leads to neurotoxicity.[161,168,178] The latter effect has led to the interest in EAA antagonists in neuropathological states, such as those following stroke.[168] The EAAs have also been shown to play a role in posttraumatic brain injury,[179] with which some of the neuropathology may be due to the excitotoxic effects of EAAs released after injury.

Currently, there are only a few drugs on the market that mediate all or part of their therapeutic effect by blocking NMDA receptors, and these are discussed below. Given the deleterious effects of excessive EAAs on neurons, there has long been an interest in developing glutamate antagonists (i.e., NMDA antagonists) to treat neuropathology. However, although these compounds appeared promising in preclinical studies, they failed to show similar benefit in patients. Moreover, the dose-limiting side effects of NMDA antagonists (e.g., psychotomimetic effects) have hindered enthusiasm for investing a huge research effort on these drugs. Nevertheless, there is still hope that the side effect problem can be overcome by using partial agonists instead of antagonists or by reducing glutamate neurotransmission at sites other than the receptor, and the search continues for new agents that will have therapeutic benefit. The ability of NMDA antagonists (e.g., ketamine and phencyclidine) to produce psychosis has led to studies examining whether activation of the NMDA receptor via the glycine coagonist site can alleviate symptoms in patients with schizophrenia. Some success has been seen.[168]

AMPA receptors can be blocked selectively by the quinoxaline diones, such as 6-nitro-7-sulphamobenzo-quinoxaline 2, 3-dione (*NBQX*), which are only used in studies involving experimental animals. However, currently there is one AMPA receptor antagonist (i.e., perampanel) available for the treatment of epilepsy.[155] *Perampanel* is an allosteric inhibitor of the glutamate-gated sodium channel and is thus a noncompetitive antagonist of the AMPA receptor. There are no selective antagonists at the kainate receptor except, perhaps, the experimental drug LY294486.

Eight different metabotropic glutamate receptors have now been cloned, which are designated as mGluR1 through mGluR8. Like other GPCRs, these have seven membrane-spanning regions but are larger (i.e., contain more amino acids) than most other GPCRs. The mGluRs are classified into three classes based on amino acid sequence homology, signal transduction mechanisms, and pharmacology: Class I includes mGluR1 and mGluR5; Class II includes mGluR2 and mGluR3; and Class III includes mGluR4, mGluR6, mGluR7, and mGluR8.[180] Several of the mGluRs are located on presynaptic nerve terminals and seem to decrease neurotransmitter release. Depending on which transmitter is released, an agonist for the mGluR can produce either excitation or inhibition.[58,168] At present, there are no clinically approved drugs that act on the mGluRs, but selective antagonists for Class I, Class II, and Class III have been identified, and it is likely that some of these drugs will be available for clinical use in the future. Class I mGluRs are linked to a G_q protein, leading to activation of the phosphatidylinositol pathway (described above), and Class II and III appear to signal through the G_i/G_o proteins, leading to a decrease in cAMP.[168,180] The mGluR2 is believed to be located presynaptically on glutamate nerve terminals where it can reduce the release of glutamate.[58] There is interest in the use of agonists and antagonists of the mGluRs in neuropsychiatric disorders, such as schizophrenia, depression, and anxiety.

Clinically useful drugs that alter excitant amino acid neurotransmission

DRUGS THAT ENHANCE THE ACTION OF GLUTAMATE

Basically, there are no clinically useful drugs that are known to enhance the action of excitant amino acids. Indeed, there are drugs and experimental compounds available for experimental studies in animals (e.g., *glutamate*, *kainate*, domoic acid, *ibotenic acid*, etc.). Many of these are convulsants and may cause excitotoxic lesions of neuronal cell bodies. Cycloserine and drugs developed for the treatment of tuberculosis are weak partial agonists at the NMDA receptor, and there is some evidence that these drugs have antipsychotic effects that can be used to treat schizophrenia. Whether agents that selectively enhance LTP in the hippocampus can be developed without the dangers of killing neurons remains to be determined.

DRUGS THAT INHIBIT THE ACTION OF GLUTAMATE

Several glutamate receptor antagonists are available for experimental work in animals, and some of these have been described previously for both the AMPA and NMDA receptors. There are only two clinically used drugs that have NMDA antagonist properties that are believed to contribute to their therapeutic effects or side effects in a significant way. These include *memantine* (Namenda®) and *ketamine*. However, there are other drugs on the market that have minor glutamate receptor antagonistic action (e.g., felbamate and amantadine) along with other effects. Glutamate receptor antagonists are of interest for treating such disorders as epilepsy, ischemic stroke, and posttraumatic brain injury. Moreover, such drugs are believed to have some potential in various neurodegenerative diseases, such as Huntington's chorea, Alzheimer's disease, Fredrick's ataxia, and others. Indeed, memantine is used to treat Alzheimer's disease. Thus, the search for new glutamate receptor blockers continues to be active research. One disappointing aspect of this work has been psychotic-like side effects that have accompanied the testing of some NMDA antagonists in humans.

It is of interest to note that the widely used drug *dextromethorphan* (DM, marketed as a cough suppressant) has also been shown to antagonize experimental seizures in animals and has been found to have some NMDA antagonist properties.[181–183] Because of all the modulatory sites on

the NMDA receptor, several drugs are known to have some antagonist effects on this receptor via a modulatory site. For example, phencyclidine (PCP, angel dust) and *ketamine* act as noncompetitive antagonists of the NMDA receptor and have psychotomimetic effects at low doses and function as dissociative anesthetics at higher doses. Although ketamine is still occasionally used as an anesthetic in human pediatric and in veterinary medicine, PCP has no approved medical use. Both are considered drugs of abuse in humans.[39] It is of interest that ketamine has recently been shown to produce a rapid reversal of symptoms in treatment-resistant patients with major depressive disorder (MDD).[184] This obviously contrasts with the delayed onset of the typical antidepressants (e.g., SSRIs). These findings have shined a new light on the role of glutamate in depression and led to much excitement regarding the potential development of new (more effective) antidepressants. A single subanesthetic dose of ketamine has been shown to alleviate depression within hours, an effect that persists for 7–10 days. The role of glutamate in depression has been tied to the current theories of synaptogenesis in the pathophysiology of depression. In this theory, it is suggested that 5-HT and NE, acting as neurotransmitters, also have the capacity to induce the synthesis and release of brain-derived neurotrophic factor (BDNF). BDNF subsequently promotes synaptogenesis. In states of depression, there is a paucity of BDNF and a retraction of synaptic structures. Augmentation of BDNF, either slowly by NE or 5-HT (typical antidepressents), or rapidly by ketamine, has the effect to reestablish or enhance synaptic connections leading to reduction of the depression.[185] Intracellular studies looking for targets on which ketamine may work have identified several, the most notable of which is mTOR (mammalian target of rapamycin). Apparently, ketamine acting through the NMDA blockade leads to the release of BDNF, which activates mTOR, and this, in turn, activates synaptogenesis, leading to a reversal of the synaptic loss seen in depression in selected brain regions (the prefrontal cortex and hippocampus).[185] There is now evidence that ketamine as well as other NMDA antagonists (e.g., memantine) can have beneficial effects in MDD as well as other mood disorders (e.g., bipolar disorder).[184,186] It seems likely that this will be an active area of investigation and drug development for some time to come.

As indicated previously, there is a recently marketed noncompetitive antagonist of the AMPA glutamate receptor (i.e., perampanel, Fycompa®) that is used to treat partial onset seizures with or without secondary generalization. This represents a novel mechanism of action for antiepileptic drugs, and we are likely to see more drugs in this category in the future. Perampanel is well-tolerated by patients but has a number of interactions with other drugs.

Glutamatergic drugs in the TBI patient

Glutamate and other excitatory amino acids have long been known to produce excitotoxic damage to neurons and glial cells and are believed to play a role in producing brain damage in the hours immediately following TBI.[178,187,188] Indeed, it has been suggested that the EAAs contribute to CNS damage in a variety of neurological disorders, such as epilepsy, stroke, and other neurodegenerative diseases.[189] Moreover, animal and human studies using microdialysis have shown the extracellular levels of glutamate are increased immediately following TBI.[189] Therefore, treatment with glutamate antagonists in the early hours following TBI should limit the damage and facilitate recovery. The only currently approved drugs that would block glutamate receptors, and potentially abort excitotoxicity, would be memantine, ketamine, and DM. Memantine has not been investigated as a treatment for human TBI (*lit search*). Ketamine has been examined to a limited extent as an anesthetic agent in the acute care of TBI patients. Despite some controversy, ketamine has been used as an anesthetic or sedative immediately following TBI. The FDA has required a warning in that older data suggested that ketamine increases intracranial pressure (ICP), which could exacerbate injury in a TBI patient. More recent data indicate that, in a controlled ventilation setting when used in combination with other sedatives, ketamine does not raise ICP.[190] Moreover, it may even provide neuroprotective effects (by blocking excitotoxicity) although the findings so far are inconclusive. DM has also been shown to produce neuroprotective effects in a rat model of projectile-induced brain injury. DM has been approved by the FDA for the treatment of pseudobulbar affect, a labile display of an emotional state (crying, laughing, etc.) that often accompanies neurodegenerative disorders and TBI. In this setting, DM is used in combination with quinidine, which inhibits the first-pass metabolism of DM and allows higher concentrations to reach the brain.[191] Memantine has been shown to reduce neuronal cell loss in the hippocampus of rats exposed to experimental TBI.[192] However, whether it would benefit human patients following TBI has not, to our knowledge, been examined.

Most of the evidence suggests that the NMDA subtype of glutamate receptor is responsible for the neuronal damage due to the increase in intracellular calcium that follows the opening of this channel.[193] Calcium, in high concentrations, can damage and kill cells.[17] Thus, administration of NMDA antagonists immediately following injury has been shown to improve recovery in rats. The hallucinogen PCP, an NMDA antagonist, was found to attenuate long-term neurobehavioral deficits in rats receiving TBI.[189] Clearly, more studies are needed in this area.

Because glutamate is involved in normal cognitive processing and in learning and memory and because it appears that glutamate release is decreased chronically after the initial increase,[189] it seems reasonable that NMDA agonists might improve cognitive function in the chronic phase following TBI. Because too much glutamate receptor activation can lead to seizures and neuron cell death, moderate or controlled activation of NMDA receptors would seem to be more useful. In this regard, the chronic administration of *cycloserine*, an NMDA partial agonist acting at the glycine site, has been shown to improve cognitive function in rats

following TBI.[194] It is of interest that D-cycloserine is an approved drug for the treatment of tuberculosis and, therefore, is available for human use. In addition, *aniracetam*, an AMPA receptor-positive allosteric modulator, has also been shown to enhance cognition in a rat model of TBI.[55] However, aniracetam is not a clinically approved drug in the United States. Another group of drugs developed along these lines (i.e., allosteric modulators) are the *ampakines*, a group of drugs that enhance AMPA receptor activity without directly activating (agonist) the receptor.[195] Ampakines appear to act by several mechanisms, one of which is to decrease the rate of receptor desensitization and deactivation, thus stabilizing the open channel of the receptor. Given that glutamate is the major fast excitatory transmitter involved in widespread cortical networks needed for learning and memory, it seems likely that enhancing or facilitating transmission throughout these networks with ampakines would enhance learning and cognitive ability and possibly the recovery of neural function in TBI. Because cognitive ability is frequently impaired following TBI, it seems worthwhile to entertain the likelihood that ampakines would be beneficial in recovery from TBI. Currently, there are no drugs of this nature on the market, but it will be of interest to see if this changes in the future because there is evidence that ampakines are learning and memory enhancers in several animal models, including nonhuman primates.[58,196] Metabotropic glutamate antagonists that block Group I mGluRs have been found to reduce neuronal degeneration in the hippocampus and behavioral deficits following TBI in rats.[197] Metabotropic glutamate agonists may also turn out to be useful in this regard. Clearly, drugs acting on glutamate receptors, both positively and negatively, can have profound effects in TBI patients and should provide some new therapeutic tools in the future.

PEPTIDE NEUROTRANSMITTERS

Until 1960, acetylcholine and the monoamines were the only well-recognized neurotransmitters. Next, GABA and the amino acids were identified as neurotransmitters in the 1960s and 1970s. The amine and amino acid neurotransmitters are sometimes referred to as the *classical* neurotransmitters. However, from 1975 to 1990, there was an explosion in the number of candidate neurotransmitters due largely to the discovery of various peptides that may function as neurotransmitters. Many of these neuroactive peptides (neuropeptides) were first discovered as hormones and were then found also to be present in neurons within the CNS. Another common finding was that many of the neuroactive peptides were also found in the gut where they served as gastrointestinal hormones. Indeed, many of these neurotransmitters were named according to their actions on the gut or other peripheral organs (e.g., vasopressin, vasoactive intestinal polypeptide, cholecystokinin).

Although one finds that the peptide neurotransmitters are not classified in any consistent manner, a common approach used by authors is based on localization. For example, peptide neurotransmitters have been grouped into the following categories: 1) the gut-brain peptides, 2) the pituitary peptides, and 3) the hypothalamic-releasing hormones.[198] Substance P is of interest because it was the first peptide neurotransmitter isolated from horse gut and brain by Euler and Gaddam[199] (although it was 40 years later before its structure was determined). Substance P is believed to be the neurotransmitter of some primary sensory afferent fibers carrying pain sensation (i.e., C-fibers), and it can be released from such nerve terminals by the active ingredient in chile peppers (i.e., *capsaicin*).[200,201] *Capsaicin* is available topically for the treatment of pain. Substance P is one of a group of interesting peptides known as *tachykinins* for which three receptors have been cloned and new antagonists are being developed.[1,172] There has been interest in tachykinin antagonists for the treatment of depression and anxiety, and several of these drugs have undergone clinical trials for depression.[1,39] The value of tachykinin antagonists as antidepressants has been unimpressive, but they do appear to have considerable value as antiemetics in cancer chemotherapy.[39]

There are far too many candidate peptide neurotransmitters to cover here. However, the opioid peptides, which mediate their effects through the receptors on which morphine and other potent narcotic analgesics act, deserve special attention. Therefore, we restrict this discussion to the opioid peptides.

Opioid peptides as neurotransmitters

The first discovered opioid peptides were the pentapeptides (containing five amino acids), leucine-enkephalin, and methionine-enkephalin, which were isolated by Hughes et al.[202] Although there may be other families of opioid peptides, current interest is focused on three separate families of opioid peptides, each derived from a separate gene family.[203] These include 1) the enkephalins (pentapeptides derived from a proenkephalin precursor), 2) the endorphins (e.g., β-endorphin, a 31 amino acid-containing peptide derived from proopiomelanocortin or POMC), and 3) the dynorphins (8 to 13 amino acid-containing peptides derived from a prodynorphin precursor). Three other endogenous opioid peptides have more recently been discovered and are known as *orphanin FQ*, *endomorphin*-1, and *endomorphin*-2. Orphanin FQ, also known as nociceptin, has effects opposite those of morphine and is referred to as *pronociceptive* (see section on opioid receptors). Much current research is focused on whether the endormorphins are selective mu agonists, but because there is relatively little known about the edomorphin peptides, we focus our discussion on the enkephalins, endorphins, and dynorphins.

Extensive maps of the enkephalin-, endorphin-, and dynorphin-containing neurons in the rat brain have been obtained using immunocytochemistry, but these are only briefly described here (see Khachaturian, Lewis, Schafer, and Watson[204] for more detail). In general, the enkephalinergic neurons are short interneurons widely distributed

throughout the neuraxis. A high density of enkephalinergic neurons is found in the basal ganglia, cerebral cortex, amygdala, and hippocampus and in such brain stem areas as the periaqueductal gray, interpeduncular nucleus, parabrachial nucleus (concerned with respiration), and the nucleus tractus solitarius as well as in the dorsal horn of the spinal cord.

The dynorphin-like immunoreactivity follows the distribution of the enkephalinergic neurons fairly closely and also appears to be found mostly in short local neurons (interneurons) rather than in long projection fibers. Thus, the enkephalin and dynorphin systems appear to be anatomically contiguous. The endorphin-containing neurons are, however, different in that they tend to be long projection neurons, which arise from the arcuate nucleus of the hypothalamus. Another area containing a high density of endorphin-containing cell bodies (called proopiomelanocortin or POMC neurons) is the pituitary gland from which β-endorphin is presumably released into the blood. The precursor of β-endorphin, POMC, is also the precursor for adrenocorticotrophic hormone (ACTH) and melanocyte stimulating hormone (α-MSH), two important pituitary hormones. Thus, depending on where in its structure POMC is cleaved by enzymes, one gets different biologically active peptides. It is little wonder, then, that the endorphins are intimately related to the endocrine system and are apparently released during stress.

Synthesis, storage, release, and inactivation of opioid peptides

The synthesis of any peptide involves transcription of the information in the genetic code of DNA (the gene) into messenger RNA (mRNA) and the translation of the message in mRNA into the appropriate sequence of amino acids in the peptide chain to form a functionally important peptide or protein. A detailed description of protein synthesis is clearly beyond the scope of this chapter, and the reader is referred to a basic textbook of biochemistry for more detail.

As indicated previously, there are three families of opioid peptides derived from different genes that lead to the synthesis of precursor proteins from which the neuroactive peptide is cleaved by the action of enzymes. Thus, proenkephalin, prodynorphin, or proopiomelanocortin (POMC) can be synthesized in the cell body of a cell that expresses these genes.

After the peptide precursors are formed, they are usually delivered to the golgi apparatus where they are packaged into neurotransmitter vesicles and then transported to the nerve terminals by axoplasmic transport. At the axon terminal, the opioid peptides are stored in vesicles from which they are released by exocytosis.[135] It is important to note that peptides cannot be synthesized at nerve terminals and must be made in the cell body and transported to the terminal for release, making them much more expensive in terms of energy expenditure.

Once the opioid or any other neuroactive peptide is released from a neuron, it is degraded by peptidases (enzymes) and cannot be recaptured by reuptake. Thus, utilization of peptides is markedly less efficient than that for the classical neurotransmitters and is, again, a more energy-expensive process. Moreover, once they are used, it will take a significantly longer time to replace them in the nerve terminal than it does for the classical transmitters.[135,205]

Another interesting aspect of peptide neurotransmitters is that they appear to be costored in neurons with other neurotransmitters, either with other peptides or the classical neurotransmitters. Examples of a classical transmitter coexisting in a neuron with a peptide include 1) serotonin and substance P, 2) dopamine and cholecystokinin, and 3) acetylcholine together with vasoactive intestinal polypeptide (VIP). In some neurons, the classical transmitter and the peptide may even be stored within the same vesicle (e.g., 5-HT and substance P).[205] However, in most cases, they are stored in separate vesicles, which are referred to as *large dense core vesicles* (LDCV), which may be three times larger in diameter than the vesicles in which classical neurotransmitters are stored, and they appear dark (dense core) in electronmicrographs of synapses.[39,206] Interestingly, the vesicles in which neuropeptides are stored are not found at the "active zone" of the nerve terminal where classical neurotransmitters dock and fuse during exocytosis. Instead, they are found in a separate pool, which, typically, is remote from the active zone and seems to require a lower concentration of calcium for release. These LDCVs seem to undergo exocytosis only after prolonged stimulation of the nerve.[39,206]

Opioid receptors

Opioid receptors were known to exist long before the discovery of the opioid peptides. Indeed, it was the discovery of opioid receptors using radioactive ligands that led to the search for the endogenous peptides by Hughes and Kosterlitz.[198] The distribution of opioid receptors was mapped before the distribution of the peptides. The opioid receptors are typically divided into three main subtypes: 1) mu (μ) receptors, 2) delta (δ) receptors, and 3) kappa (κ) receptors. More recently, a new receptor related to the opioid receptors was cloned. Because it had a high degree of homology (similarity) to other opioid receptors but was unresponsive to endogenous opioid peptides (enkephalins, endorphins, dynorphins), it was referred to as an *orphan* receptor. Subsequently, a novel endogenous peptide ligand for the orphan receptor was isolated and sequenced. This peptide appeared to have nociceptive effects (i.e., cause pain) when bound to the orphan receptor. Thus, the ligand was named *nociceptin/orphanin FQ*. Now, there appears to be a family of these peptides, and they all bind to GPCRs (i.e., G_i/G_o).[39,207] The functional significance of the nociceptin/orphanin FQ system is not entirely known, but there is interest in developing antagonists for these receptors because they could be useful in the treatment of pain. The receptor for nociception/ophanin FQ (i.e., the fourth subtype of opioid receptor) is called the nociception/orphanin

FQ receptor or NOP-R, and it acts to produce pronociception in some regions of the CNS and analgesia in others.[58]

Mu receptors appear to be the primary receptors involved in mediating analgesia and, therefore, have a high affinity for morphine and related drugs. The endorphins have a higher affinity for mu receptors than for any other opiate receptor subtypes. Indeed, the rank-order potency of agonists for opioids binding to the mu receptor is β-endorphin > morphine > met-enkephalin > leu-enkephalin > dynorphin.

The mu receptor is believed to be a 65 kDa protein with a widespread distribution in the CNS.[208] The density of mu receptors is high in the striatum, amygdala, cortex, periaqueductal gray regions of the midbrain, and thalamus.[209] Mu receptors are also found in the periphery. The mu receptor is a G-protein linked receptor that is negatively coupled with cAMP (i.e., a G_i protein) and is involved in mediating hyperpolarization by opening K^+ channels.[209]

The use of mu agonists can alleviate opiate withdrawal syndrome. Beta-endorphin is the naturally occurring endogenous ligand for the mu receptor. *Morphine*, derived from a plant (Papver somniferum), and its analogs also mediate most of their effects through the mu receptor. *Naloxone* (Narcan®) is a potent antagonist of the mu opioid receptor that is widely used for the treatment of opioid overdose.

The delta receptor binds leu-enkephalin with a greater affinity than met-enkephalin, β-endorphin, or morphine. Thus, the enkephalins are believed to be the natural ligands for the delta receptor.[171] The distribution of δ receptors corresponds closely to the distribution of enkephalin neurons and, like the mu receptors, are linked to adenylate cyclase in a negative fashion via a G_i protein.[208] Naloxone is a less potent antagonist at delta receptors than it is at mu receptors.

The kappa opioid receptors bind *pentazocine* (Talwin®), *butorphanol* (Stadol®), *nalbuphine* (Nubain®), and *buprenorphine* (Buprenex®), which are all clinically approved kappa receptor agonists with variable effects on the mu opioid receptor. The natural ligand for the kappa receptor is the endogenous opioid peptide dynorphin. The density of kappa receptors is highest in the spinal cord and brain stem. Naloxone can act as an antagonist at kappa receptors, but it is less potent than at mu receptors. Kappa agonists cannot alleviate the symptoms of opioid withdrawal. However, stimulation of kappa receptors can alleviate pain, especially viscerally mediated chemical pain.[208] As mentioned, dynorphin is believed to be the natural agonist for the kappa receptor, and dynorphin levels are increased in the brain immediately following TBI. Interestingly, animal research has shown that kappa agonists may actually increase neurological deficits when administered following TBI (see section on opioids in the TBI patient). A major goal of opioid research has long been to find analgesic drugs with the efficacy of opioids but which do not produce tolerance, dependence, and addiction. It was believed that gaining an understanding of what causes tolerance would help accomplish this goal because tolerance and physical dependence seem to go hand in hand. Unfortunately, understanding the mechanism of tolerance to these drugs has been challenging and remains controversial. Currently, studies concerning opioid tolerance are focused on the trafficking of opioid receptors between an intracellular compartment and the cell membrane. When morphine tolerance develops, the total number of receptors in and on the cell does not change. However, the trafficking of receptors between the intracellular compartment and the cell membrane does change. Apparently when agonists bind to them, mu opioid receptors (MORs) first undergo desensitization via phosphorylation by receptor kinases, and these desensitized receptors then undergo endocytosis into the cell where they are resensitized and then recycled to the membrane to maintain sensitivity under conditions of acute morphine administration.[210,211] With chronic use, there is evidence that morphine increases the expression of delta opioid receptors (DORs), which are mainly found in large dense core vesicles within the cytosol.[212,213] However, DORs also get inserted into the plasma membrane where they can interact with the MORs and even form heterodimers. The increase in DORs in the membrane seems to negatively influence the MORs by preventing endocytosis and resensitization. So the failure of chronic morphine to induce endocytosis of the MOR is believed to play an important role in the development of tolerance.[209–213] It has therefore been speculated that drugs or agents that prevent the membrane expression of DORs would prevent the development of tolerance to morphine and other mu agonists. It will be interesting to see if support for the latter hypothesis can be obtained in the future.

Clinically useful drugs that alter opioid neurotransmission

DRUGS THAT ENHANCE OPIOIDERGIC NEUROTRANSMISSION

Opioid agonists

A comprehensive discussion of the pharmacology of opioid agonists and antagonists has been provided by Yaksh and Wallace[214] and is beyond the scope of this chapter. The agonists are the only available drugs for enhancing opioidergic neurotransmission. These are the narcotic analgesics used to treat severe pain, such as that occurring postoperatively. *Morphine* is the prototypical drug in this class and has been around since 1806. It is a natural constituent of opium powder but can now be made in the chemistry laboratory. *Meperidine* (Demerol®) is a synthetic analog of morphine widely used in hospitals for postoperative pain. Both of these are primarily mu agonists but also have some agonist activity at delta and kappa receptors. *Codeine*, the *o*-methyl analog of morphine, has similar properties but is a weaker agonist because it must be converted to morphine in the liver, and only 10% of the codeine undergoes this conversion. Indeed, the analgesic effects of codeine are believed to be mediated by newly formed morphine.

Pentazocine (Talwin®) is a kappa agonist and a partial mu agonist, and *butorphanol* (Stadol®) has similar properties.

Pentazocine was originally marketed as a nonnarcotic analgesic, but this error was eventually corrected. *Buprenorphine* (Buprenex®) is a long-acting partial mu agonist. *Nalbuphine* is a kappa agonist and mu antagonist with analgesic effects. The latter drugs are often referred to as *mixed agonist-antagonists*. These drugs produce less respiratory depression and have less risk of dependence than the full agonists. Thus, they are considered safer to use as analgesics.

Opioid analgesics have many side effects, not the least of which is respiratory depression, which can kill the patient in overdose. If recognized early, this can be easily reversed by opioid antagonists (see the following). Opioid analgesics, especially codeine, are also very useful to suppress the cough reflex and are commonly added to cough mixtures (syrups).

DRUGS THAT INHIBIT OPIOIDERGIC NEUROTRANSMISSION

Opioid antagonists

Naloxone (Narcan®) is a nonselective opioid antagonist that is used to treat life-threatening overdoses of opioid analgesics. It functions as an antagonist at mu, delta, and kappa receptors and must be given parenterally (not by mouth). The administration of 0.4 to 0.8 mg intravenously or intramuscularly can reverse the effects of mu opioid agonists in humans and will precipitate a withdrawal syndrome in addicted individuals.[214] *Naltrexone* (Trexan®) is also a nonselective narcotic antagonist with oral efficacy and a longer duration of action, allowing it to be administered orally. Naltrexone is approved for the treatment of alcoholism for which it apparently reduces craving. It is also available in a combination product marketed under the name of Contrave® (naltrexone + *bupropion*) for the treatment of obesity. Indeed, the importance of opioids acting through dopamine neurons to regulate food intake is an active area of research.[58]

Opioids in the TBI patient

There is evidence in the experimental literature that endogenous opioids, acting through kappa receptors, may be detrimental to recovery of function following TBI and may exacerbate the actual injury that follows. An increase in dynorphin (kappa agonist) has been demonstrated following TBI in an animal model of brain injury,[215] and kappa receptor agonists have been shown to increase neurologic deficits after experimentally induced spinal cord injury in rats. Moreover, kappa antagonists have been found to reverse deficits associated with spinal cord injury.[216] Kappa agonists may, in fact, facilitate neuronal damage via an action through glutamate because NMDA antagonists were found to reverse the neurotoxicity associated with dynorphin in the spinal cord injury model.[217]

Alternatively, although activation of kappa receptors appears to enhance neurologic damage, activation of mu and delta opioid receptors may be neuroprotective rather than neurotoxic.[218] Thus, it appears that, immediately following injury, administering a kappa antagonist or a mu agonist could be beneficial in reducing neurological damage associated with TBI. However, more research is needed to determine if these findings might be applicable in humans and, if so, the appropriate timing, dose, and other parameters needed to reduce neurological deficits.

Other uses of opioids in the TBI patient obviously include their use as analgesics to alleviate pain while recovering from multiple injuries (that often accompany the TBI). However, when using opioids as analgesics, it is important for practitioners to be cognizant of possible detrimental effects that can also occur. Knowledge of the specific receptors on which the drugs act and the selection of specific mu or delta agonists may prevent such detrimental effects.

SUMMARY

The preceding pages provide considerable detail concerning the process of neurotransmission in the nervous system. It is clear that neurotransmission is the fundamental basis of communication between neurons of the various brain areas. Virtually any of the players in neurotransmission are potential sites of modulation and neuroplasticity in the context of brain injury (and recovery). Additionally, neurotransmission is the principal target for drugs that affect the nervous system. Although it is impossible to provide a concise summary of the broad array of topics covered in this chapter, the editor felt that some type of summary of the clinically relevant drugs showing the neurotransmitters through which they exert their action would be useful for the busy practitioner, and we fully agree. Therefore, an appendix (see Appendix 16-A) has been provided at the end of this chapter to summarize these relationships and to give the reader a quick mechanism for linking the drugs to the neurotransmitters. It should be noted, however, that we have only included the drugs discussed in this chapter. Although they represent some of the more popular ones in use today, they are by no means the only ones available. Practitioners of rehabilitation as well as other specialties in medicine must be aware that pharmacology is a constantly changing field with new drugs being introduced every month. It is hoped that this chapter also provides a foundation that will allow the reader to appreciate and understand the mechanism of action of new (undiscovered) drugs that will be introduced in the future.

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APPENDIX 16-A: SUMMARY OF RELATIONSHIP BETWEEN THERAPEUTICALLY USED DRUGS AND VARIOUS NEUROTRANSMITTERS

Drug name	Brand name[a]	Neurotransmitter	Receptor	Drug action
Acebutolol	Sectral	NE	$Beta_1$	Beta-1 receptor blocker
Acetylcholine	Miochol-E (Ophthalmic)	ACh	Nicotinic and muscarinic-cholinergic	Agonist for muscarinic and nicotinic receptors
Albuterol	Proventil	Epinephrine (hormone)	$Beta_2$	Beta-2 receptor agonist
Almotriptan	Axert	Serotonin	$5\text{-}HT_{1D/1B}$	Serotonin 1D/1B receptor agonist
Alosetron	Lotronex	Serotonin	$5\text{-}HT_3$	Blocks $5\text{-}HT_3$ receptors
Alpha-methyltyrosine	Demser	Dopamine, NE	–	Blocks synthesis of dopamine and NE
Alprazolam	Xanax	GABA	Benzodiazepine-$GABA_A$ complex	Agonist for benzodiazepine receptor
Amantadine	Symmetrel	Dopamine	–	Increases release and blocks reuptake of dopamine
Amphetamine/ dextroamphetamine	Adderall	Dopamine; NE	–	Increases release and blocks reuptake of NE and dopamine
Apomorphine	Apokyn	Dopamine	D-1 and D-2 dopamine	Agonist for D-1 and D-2 receptors
Aripiprazole	Abilify	Dopamine, 5-HT	D-2, $5\text{-}HT_{2A}$	Partial D-2 agonist, $5\text{-}HT_{2A}$ antagonist
Asenapine	Saphris	Dopamine, 5-HT	D-2/D-4, $5\text{-}HT_{2A}$	D-2/D-4 and $5\text{-}HT_{2A}$ antagonist
Atenolol	Tenormin	NE	$Beta_1$	Blocks beta-1 receptors
Atomoxetine	Strattera	NE	–	NE uptake blocker
Atracurium	Generic	ACh	Nicotinic ACh	Blocks nicotinic receptor at NMJ
Atropine	Atropine Sulfate	ACh	Muscarinic-cholinergic	Blocks muscarinic receptors
Baclofen	Lioresal	GABA	$GABA_B$	Agonist for $GABA_B$ receptors
Benztropine	Cogentin	ACh	Muscarinic-cholinergic	Blocks muscarinic receptors
Bethanechol	Urecholine	ACh	Cholinergic-muscarinic	Agonist for muscarinic receptor
Bretylium	Bretylium Tosylate	NE	–	Blocks release of NE
Bromocriptine	Parlodel	Dopamine	Dopamine (D-1, D-2, etc.)	Nonselective dopamine receptor agonist
Buprenorphine	Buprenex	β-endorphin; enkephalin	Opioid (mu)	Partial agonist for mu receptor and a kappa antagonist
Bupropion	Wellbutrin; Zyban	Dopamine	–	Blocks reuptake of dopamine
Buspirone	Buspar	Serotonin (5-HT)	$5\text{-}HT_{1a}$	Partial agonist for $5\text{-}HT_{1a}$ receptor
Butorphanol	Stadol	β-endorphin; enkephalin	Kappa and mu opioid	Kappa agonist and partial mu agonist

(*Continued*)

Drug name	Brand name[a]	Neurotransmitter	Receptor	Drug action
Capsaicin	Zostrix-HP	Substance P	–	Depletes C-fibers (pain fibers) of Substance P; used as topical analgesic
Carbachol	Isopto Carbachol	ACh	Muscarinic-cholinergic; nicotinic-cholinergic	Muscarinic and nicotinic agonist
Cevimeline	Evoxac	ACh	Muscarinic M3	Muscarinic M3 agonist
Chlorpromazine	Thorazine	Dopamine	Dopamine D-2	Blocks dopamine receptors
Clorazepate	Tranxene	GABA	Benzodiazepine	Benzodiazepine agonist
Citalopram	Celexa	Serotonin	–	Blocks serotonin reuptake
Clomipramine	Anafranil	Serotonin	–	Blocks serotonin reuptake
Clonazepam	Klonopin	GABA	Benzodiazepine-$GABA_A$ complex	Benzodiazepine agonist
Clonidine	Catapres	NE	$Alpha_2$	Alpha-2 agonist
Clozapine	Clozaril	Dopamine	Dopamine D-2; $5\text{-}HT_{2A}$	Blocks D-2 and $5\text{-}HT_{2A}$ receptors
Cocaine	Cocaine HC1	NE; dopamine	–	Blocks reuptake of NE and dopamine
Codeine	Found in many cough syrups and analgesics containing acetaminophen	ß-endorphin; enkephalin	Opioid (mu)	Agonist for mu and delta opioid receptors
Cycloserine	Seromycin	Glutamate	NMDA	NMDA partial agonist
d-tubocurarine	Tubocurarine chloride	ACh	Nicotinic-cholinergic	Nicotinic receptor blocker
Desipramine	Norpramin	NE	–	Blocks NE reuptake
Desvenlafaxine	Pristiq	NE, 5-HT	–	Selective NE and 5-HT reuptake inhibitor (SNRI)
Dextroamphetamine	Dexedrine, Adderall	NE; dopamine	–	Increases release of NE and dopamine and blocks reuptake
Dextromethorphan	Found in many cough syrups (e.g., Robitussin-DM)	Glutamate	NMDA	Blocks glutamate NMDA receptor
Diazepam	Valium	GABA	Benzodiazepine-$GABA_A$ complex	Agonist for benzodiazepine receptor
Disulfiram	Antabuse	NE	–	Blocks synthesis of NE
Dobutamine	Dobutrex	NE	$Beta_1$ adrenergic receptor	Agonist for $Beta_1$ receptors
Dolasetron	Anzemet	Serotonin	$5\text{-}HT_3$	Blocks $5\text{-}HT_3$ receptors
Donepezil	Aricept	ACh	–	Blocks enzymatic breakdown of ACh
Doxazosin	Cardura	NE	Alpha-1 adrenoceptor	Blocks alpha-1 adrenoceptors
Duloxetine	Cymbalta	NE, 5-HT	–	SNRI
Edrophonium	Tensilon	ACh	–	Cholinesterase inhibitor; prevents degradation of ACh
Eletriptan	Relpax	Serotonin	$5\text{-}HT_{1D/1B}$	Agonist for $5\text{-}HT_{1D/1B}$ receptor

(*Continued*)

Drug name	Brand name[a]	Neurotransmitter	Receptor	Drug action
Entacapone	Comtan	NE; dopamine	–	Blocks enzymatic breakdown of NE and dopamine by blocking COMT
Escitalopram	Lexapro	Serotonin	–	Blocks serotonin reuptake
Esmolol	Brevibloc	NE	$Beta_1$ adrenergic	Blocks $Beta_1$ receptor
Eszopiclone	Lunesta	GABA	Benzodiazepine-$GABA_A$ complex	Benzodiazepine receptor agonist
Fenfluramine	Pondamin	Serotonin	–	Increases the release of serotonin
Flumazenil	Romazicon	GABA	Benzodiazepine-$GABA_A$ complex	Blocks benzodiazepine receptor
Fluoxetine	Prozac	Serotonin	–	Blocks reuptake of serotonin
Flurazepam	Dalmane	GABA	Benzodiazepine-$GABA_A$ complex	Facilitates the action of GABA
Fluvoxamine	Luvox	Serotonin	–	Blocks serotonin reuptake
Frovatriptan	Frova	Serotonin	5-$HT_{1D/1B}$	Agonist for 5-$HT_{1D/1B}$ receptor
Galantamine	Razadyne	ACh	–	Blocks enzymatic breakdown of ACh
Glycopyrrolate	Robinul	ACh	Muscarinic	Blocks muscarinic receptors
Granisetron	Kytril	Serotonin	5-HT_3	Blocks 5-HT_3 receptors
Guanabenz	Wytensin	NE	$Alpha_2$	Alpha-2 agonist
Guanadrel	Hylorel	NE	–	Blocks the release of NE
Guanethidine	Ismelin	NE	–	Blocks the release of NE
Guanfacine	Tenex	NE	$Alpha_2$ adrenergic	Alpha-2 agonist
Haloperidol	Haldol	Dopamine	Dopamine D_2	Blocks dopamine receptors
Iloperidone	Fanapt	Dopamine, 5-HT	D-2; 5-HT_{2A}	Blocks D-2 and 5-HT_{2A} receptors
Ipratropium	Atovent	ACh	Muscarinic-cholinergic	Muscarinic blocker
Isocarboxazid	Marplan	NE; dopamine; serotonin	–	Inhibits degradative enzyme (monoamine oxidase)
Isoproterenol	Isuprel	NE	$Beta_1$ and $Beta_2$ adrenergic	Agonist for all beta receptors
Ketamine	Ketalar	Glutamate	NMDA	Noncompetitive blocker of NMDA receptor
L-DOPA and carbidopa	Sinemet	Dopamine	–	Increases synthesis of dopamine
Levodopa	Larodopa	Dopamine	–	Increases synthesis of dopamine
Levomilnacipran	Fetzima	NE, 5-HT	–	SNRI
Lorazepam	Ativan	GABA	Benzodiazepine-$GABA_A$ complex	Agonist for benzodiazepine receptor
Lurasidone	Latuda	Dopamine, 5-HT	D-2; $5HT_{2A}$	Blocks D-2 and 5-HT_{2A} receptors

(*Continued*)

Drug name	Brand name[a]	Neurotransmitter	Receptor	Drug action
Maprotiline	Ludiomil	NE	–	NE reuptake inhibitor
Mecamylamine	Inversine	ACh	Nicotinic-cholinergic	Blocks neuronal nicotinic receptors
Memantine	Namenda	Glutamate	NMDA	Blocks NMDA receptors
Meperidine	Demerol	β-endorphin; enkephalin	Opioid (mu)	Agonist at mu opioid receptors
Metaproterenol	Metaprel	NE	$Beta_2$	Selective agonist for beta-2 receptor
Metaraminol	Aramine	NE	$Alpha_1$	Agonist for alpha-1 receptors
Methacholine	Provocholine	ACh	Muscarinic-cholinergic	Agonist for muscarinic receptors
Methamphetamine	Desoxyn	NE and dopamine	–	Increases release of NE and dopamine
Methoxamine	Vasoxyl	NE	$Alpha_1$	Agonist for alpha-1 receptor
Methylphenidate	Ritalin	Dopamine and NE	–	Increases release of dopamine and NE
Methysergide	Sansert	Serotonin	Serotonin	Nonselective serotonin receptor blocker
Metoclopramide[b]	Reglan	Dopamine; serotonin	Dopamine D_2; 5-HT_3	Blocks dopamine D–2 and 5-HT_3 receptors
Metoprolol	Lopressor	NE	$Beta_1$	Blocks beta-1 receptors
Milnacipran	Savella	NE, 5-HT	–	SNRI
Molindone	Moban	Dopamine	Dopamine D_2	Blocks dopamine receptors
Morphine	Morphine Sulfate	β-endorphin	Mu opioid	Agonist for mu receptor
Nalbuphine	Nubain	Dynorphin	Kappa and mu opioid	Kappa agonist; mu antagonist
Naloxone	Narcan	β-endorphin; enkephalin	Opioid	Nonselective opioid receptor blocker
Naltrexone	Trexan	β-endorphin; enkephalin	Opioid	Nonselective opioid receptor blocker
Naratriptan	Amerge	Serotonin	5-$HT_{1D/1B}$	Serotonin receptor 1B/1D agonist
Neostigmine	Prostigmin	ACh	–	Blocks degradation of ACh by cholinesterase
Nicotine	Nicoderm (patch); Nicorette (gum)	ACh	Nicotinic-cholinergic	Agonist for nicotinic receptor
Norepinephrine	Levophed	NE	$Alpha_1$, $alpha_2$, $beta_1$	Agonist for adrenergic receptors
Nortriptyline	Aventyl	NE	–	Blocks reuptake of NE
Olanzapine	Zyprexa	Dopamine; serotonin	Dopamine $D_{2/4}$, 5-HT_{2A}	Blocks dopamine and serotonin receptors
OnabotulinumtoxinA	Botox	ACh	–	Blocks release of ACh
Ondansetron	Zofran	Serotonin	5-HT_3	Blocks 5-HT_3 receptor
Oxazepam	Serax	GABA	Benzodiazepine-$GABA_A$ complex	Agonist for benzodiazepine receptor

(*Continued*)

Drug name	Brand name[a]	Neurotransmitter	Receptor	Drug action
Paliperidone	Invega	Dopamine, 5-HT	Dopamine $D_{2/4}$; 5-HT_{2A}	Blocks D2/D4 and 5-HT_{2A} receptors
Pancuronium	Pavulon	ACh	Nicotinic-cholinergic (at neuromuscular junction)	Blocks nicotinic receptor
Paroxetine	Paxil	Serotonin	–	Blocks serotonin reuptake
Pentazocine	Talwin	β-endorphin; enkephalin	Mu opioid; kappa opioid	Mu antagonist; kappa agonist
Pentobarbital	Nembutal	GABA	$GABA_A$	Facilitates action of GABA
Perampanel	Fycompa	Glutamate	AMPA (glutamate)	Blocks AMPA receptors
Pergolide	Permax	Dopamine	Dopamine D_1 and D_2	Agonist for D_1 and D_2 receptors
Perphenazine	Trilafon	Dopamine	Dopamine D_2	Blocks dopamine receptors
Phenelzine	Nardil	NE; dopamine; serotonin	–	Blocks monoamine oxidase to prevent degradation of monoamine transmitters
Phenobarbital	Luminal	GABA	$GABA_A$	Facilitates action of $GABA_A$
Phenoxybenzamine	Dibenzyline	NE	$Alpha_1$, $alpha_2$	Irreversibly blocks alpha-1 and alpha-2 receptors
Phentolamine	OraVerse	NE	$Alpha_1$, $alpha_2$	Reversibly blocks alpha-1 and alpha-2 receptors
Phenylephrine	Neo-Synephrine	NE	$Alpha_1$	$Alpha_1$ adrenoceptor agonist
Physostigmine	Generic	ACh	–	Blocks enzymatic breakdown of ACh
Pilocarpine	Salagen	ACh	Muscarinic-cholinergic	Muscarinic agonist
Pindolol	Visken	NE	$Beta_1$ and $beta_2$	Blocks beta adrenergic receptors
Pirenzepine	Gastrozepine (available in Europe)	ACh	M_1 muscarinic	Blocks M1 receptors
Pramipexole	Mirapex	Dopamine	Dopamine D_1, D_2	Agonist for dopamine receptors
Prazosin	Minipress	NE	$Alpha_1$	Blocks alpha-1 receptor
Primidone	Mysoline	GABA	$GABA_A$	Facilitates action of $GABA_A$
Prochlorperazine	Compazine	Dopamine	Dopamine D_1 and D_2	Blocks D–1 and D–2 receptors
Propofol	Diprivan	GABA	$GABA_A$	Facilitates action of GABA
Propranolol	Inderal	NE	$Beta_1$ and $beta_2$	Blocks beta-1 and beta-2 receptors
Protriptyline	Vivactil	NE	–	Blocks reuptake of NE
Pyridostigmine	Mestinon	ACh	–	Blocks enzymatic breakdown of ACh
Quazepam	Doral	GABA	Benzodiazepine-$GABA_A$ complex	Agonist for benzodiazepine receptor
Quetiapine	Seroquel	Dopamine; serotonin	Dopamine $D_{2/4}$, 5-HT_{2A}	Blocks dopamine and serotonin receptors
Rasagiline	Azilect	Dopamine	–	Inhibits monoamine oxidase Type B

(*Continued*)

Drug name	Brand name[a]	Neurotransmitter	Receptor	Drug action
Reserpine	Generic	NE; dopamine; serotonin	–	Blocks storage of monoamine transmitter and depletes nerves
Risperidone	Risperdal	Dopamine; serotonin	Dopamine $D_{2/4}$, 5-HT_{2A}	Blocks dopamine and serotonin receptors
Rivastigmine	Exelon	ACh	–	Blocks enzymatic breakdown of ACh
Rizatriptan	Maxalt	Serotonin	5-$HT_{1D/1B}$	Serotonin receptor 1B/1D agonist
Ropinirole	Requip	Dopamine	Dopamine D_1, D_2	Dopamine receptor agonist
Rotigotine	Neupro	Dopamine	Dopamine D_1, D_2, D_3	Agonist for dopamine receptors
Scopolamine (hyoscine)	Isopto Hyoscine	ACh	Muscarinic-cholinergic	Muscarinic blocker
Secobarbital	Seconal	GABA	$GABA_A$	Facilitates action of $GABA_A$
Selegiline	Eldepryl, Emsam	Dopamine	–	Inhibits monoamine oxidase Type B, which degrades dopamine
Sertraline	Zoloft	Serotonin	–	Serotonin reuptake inhibitor
Sotalol	Betapace	NE	$Beta_1$ and $beta_2$	Beta-1 and beta-2 blocker
Succinylcholine	Anectine	ACh	Nicotinic-cholinergic (at neuromuscular junction)	Nicotinic receptor blocker
Sumatriptan	Imitrex	Serotonin	5-$HT_{1D/1B}$	Agonist for 5-$HT_{1D/1B}$ receptors
Tacrine	Cognex	ACh	Nicotinic and muscarinic-cholinergic	Cholinesterase inhibitor; partial agonist at muscarinic receptors
Temazepam	Restoril	GABA	Benzodiazepine-$GABA_A$ complex	Agonist for benzodiazepine receptor
Terazosin	Hytrin	NE	$Alpha_1$	Alpha-1 blocker
Terbutaline	Brethine	NE	$Beta_2$	Agonist at beta-2 receptor
Tetrabenazine	Xenazine	NE, dopamine, 5-HT	–	Blocks storage of NE, dopamine, and 5-HT in vesicle (depletes nerves of transmitter)
Thioridazine	Mellaril	Dopamine	Dopamine D_2	Blocks dopamine receptors
Thiothixene	Navane	Dopamine	Dopamine D_2	Blocks dopamine receptors
Tiagabine	Gabitril	GABA	–	Blocks GABA uptake
Tiotropium	Spiriva	ACh	Muscarinic M3	Blocks muscarinic M3 receptors
Tolcapone	Tasmar	NE; dopamine	–	Blocks enzymatic breakdown of NE and dopamine by blocking COMT
Tranylcypromine	Parnate	NE; serotonin; dopamine	–	Inhibits degradation of monoamines by monoamine oxidase
Triazolam	Halcion	GABA	Benzodiazepine-$GABA_A$ complex	Agonist for benzodiazepine receptor

(*Continued*)

Drug name	Brand name[a]	Neurotransmitter	Receptor	Drug action
Trimethaphan	Arfonad	ACh	Nicotinic-cholinergic (at autonomic ganglia)	Blocks nicotinic receptor
Valproic acid	Depakene	GABA	–	Increases synthesis and blocks degradation of GABA
Varenicline	Chantix	ACh	Nicotinic cholinergic in brain	Partial agonist for nicotinic receptor
Vecuronium	Norcuron	ACh	Nicotinic-cholinergic (at neuromuscular junction)	Blocks nicotinic receptor
Venlafaxine	Effexor	NE, 5-HT	–	SNRI
Vigabatrin	Sabril	GABA	–	Blocks GABA degradation (GABA-T inhibitor)
Vortioxetine	Brintellix	5-HT	5-HT_1, 5-HT_3, 5-HT_7	$5\text{-HT}_{1A/1B}$ partial agonist; 5-HT_{1D}, 5-HT_3, 5-HT_7 antagonist (serotonin modulator)
Zaleplon	Sonata	GABA	Benzodiazepine -$GABA_A$ complex	Agonist for benzodiazepine receptor
Ziprasidone	Geodon	Dopamine; serotonin	Dopamine $D_{2/4}$, 5-HT_{2A}	Blocks dopamine and serotonin receptors
Zolmitriptan	Zomig	Serotonin	$5\text{-HT}_{1D/1B}$	Serotonin receptor 1B/1D agonist
Zolpidem	Ambien	GABA	Benzodiazepine-$GABA_A$ complex	Agonist for benzodiazepine receptor

Abbreviations: 5-HT, 5-hydroxytryptamine; ACh, acetylcholine; COMT, catechol-O-methyltransferase; GABA, gamma aminobutyric acid; NE, norepinephrine; NMDA, *N*-methyl-*D*-aspartate; NMJ, neuromuscular junction; SNRI, selective NE and 5-HT reuptake inhibitor.

[a] Includes only one example of a brand name.

[b] See Table 16.4 for other dopamine receptor antagonists.

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Pituitary dysfunction after traumatic brain injury

TIFFANY GRECO

INTRODUCTION

Traumatic brain injury (TBI) is the leading cause of death and disability.[1] Main causes include falls, blunt trauma, and motor vehicle accidents.[2] War accidents, although not included in CDC data, account for a significant amount of brain injuries per year.[3] Contact/collision sports have emerged as sources of repetitive head trauma and may result in cumulative pituitary damage.[4] TBI has long been recognized as a cause of hypopituitarism; although it was initially considered to be a rare event with only 367 cases being reported prior to 2000.[5] The first study reporting pituitary dysfunction was in 1918 by Cyran,[6] and a subsequent study found only a 0.7% incidence following injury.[7] Over the past half century, individual case reports and literature reviews have brought attention to the subject. Early pathophysiological studies showed up to a third of deceased TBI patients had some level of necrotic pituitary injury.[8–11] Continued retrospective and prospective studies now place incidence between 16% and 61%[12] in children and 15% to 68% in adults,[13] clearly demonstrating hypopituitarism is an underdiagnosed and undertreated complication following TBI.

Survivors of TBI often have complaints regarding neurobehavior and quality of life (QoL). Common symptoms include memory and concentration deficits; impaired judgment, decision making, and problem solving; depression; anxiety; fatigue; malaise; and loss of libido.[14–18] These symptoms overlap with those reported by patients with hypopituitarism and may be due to endocrinologic deficits rather than the TBI itself.[19,20] This overlap in symptoms can complicate diagnosis. Timing of symptoms may further complicate diagnosis. Most patients present with symptoms and hypopituitarism acutely following injury with the majority having resolution within the first 3–6 months; however, a certain subset of patients may continue to have chronic symptoms or may not present with symptoms until months after the injury and then continue to decline.[21] The most often affected hormones are growth hormone (GH) and the gonadotropins,[21] and they appear to be due to the unique anatomical vulnerability of the anterior pituitary to damage following TBI.

Another facet of hormones is their role in brain development and recovery following TBI. Hormones play a significant role in the development of specific brain structures and organization and activation of neural circuitry.[22–24] Disruption of hormones during neonatal and adolescent developmental

periods results in permanent structural changes within the brain that have negative consequences on function and behavior as adults. This is of significant importance as the highest rates of TBI occur in these two age groups.[25]

Beyond development, hormones are involved in several biological activities within the brain that include, but are not limited to, neuronal plasticity, neurogenesis, synaptogenesis, neuronal survival, angiogenesis, myelination, and excitatory and inhibitory neurotransmission.[22,26–30] These same basic functions play a key role in recovery after TBI when hormones then act as neuroprotective and neurotrophic factors. Awareness of hypopituitarism following TBI remains poor and should be an issue of high priority given the personal and socioeconomic burden of TBI. Further studies are needed to determine better screening and treatment protocols such that patient recovery and rehabilitation can be improved.

PREVALANCE OF TBI-INDUCED HYPOPITUITARISM

Adults

TBI-induced hypopituitarism was first reported in 1918 in a patient with a basilar skull fracture.[6] Altman and Pruzanski published the first review paper on the subject in 1961, and it described 21 patients.[31] This was followed by a second review in 1986 that comprised a total of 53 patients.[32] The 1942 publication by Escamilla and Lisser observing causes of hypopituitarism showed only four in 595 cases (0.7%) were caused by head trauma[7] despite several autopsy studies between 1959 and 1971 showing up to a third of TBI patients with hypothalamic and/or pituitary lesions.[8–11] In 2000, Benvenga et al. authored a third review, which had a total of 367 patients. In that review, the prevalence of gonadotropin, adrenocorticotropic hormone (ACTH), thyroid-stimulating hormone (TSH), and GH deficiencies and hyperprolactinemia were 100%, 52.8%, 44.3%, 23.7%, and 47.7%, respectively.[5] This and the study done by Kelly et al. in 2000 showing 40% of head injury had some kind of hormone affected helped increase research interest in the field;[33] between 2000 and 2005, an additional 192 cases were added.[34]

Since 2000, several retrospective and prospective studies have shown that TBI-induced hypopituitarism is not as rare as once thought. Currently, the frequency of hypopituitarism ranges from 5.4% to 90%.[33,35–37] A 2007 meta-analysis of 1,137 TBI patients from 10 cross-sectional and four prospective studies reported an incidence range of 15%–68% and a pooled prevalence of any hormone deficiency as 25.7%.[38] Degree and type of pituitary deficiency varied between studies although GH and gonadotropin (luteinizing hormone/follicle-stimulating hormone [LH/FSH]) was the most common. GH incidence ranged from 2% to 68% with a pooled prevalence of 28% 5 years after injury. Schneider et al. also stratified results based on severity of injury and found the pooled prevalence of hypopituitarism in mild, moderate, and severe TBI was estimated to be 16.8%, 10.9%, and 35.3%, respectively.[13] Although these data show hypopituitarism was more common in severe TBI, the risk of developing pituitary dysfunction following mild TBI (mTBI) is still high. A more recent 2014 meta-analysis of 5,386 patients from 66 studies, including prospective/retrospective, case control, cross-sectional studies and randomized trials, found pooled prevalence in low biased studies of TBI-induced hypopituitarism to be 65.3%, 36%, and 33.1% at ≤3 months, 3–12 months, and ≥12 months, respectively.[39] Similar to Schneider's 2007 study, GH and gonadotropin were the two most affected axes. Pooled prevalence for GH was 35.5%, 12.4%, and 14.6% at ≤3 months, 3–12 months, and ≥12 months, respectively. Pooled prevalence for gonadotropin was 59.5%, 19.7%, and 9.8% at ≤3 months, 3–12 months, and ≥12 months, respectively. They also found age at time of injury, injury severity, and skull fracture were predictors of anterior pituitary dysfunction; however, none of these predictors were significant when only studies with low bias were included.[40] Variability in hypopituitarism prevalence can depend on many factors, including severity of injury, timing of hormone evaluation, study design, kind of injury, study population, and diagnostic methods.

Children

TBI-induced hypopituitarism has been well described in adult patients, but these effects have not been addressed in the juvenile population despite similar prevalence (16%–61%, 1–5 years postinjury).[12] Long-term complications are similar to those in adults and include poor memory; motor deficits; and emotional, behavioral, and social disturbances with 40% of children suffering from decreased QoL 1 year after injury.[41] In addition to the symptoms listed here, the juvenile population is uniquely vulnerable to hypopituitarism as pituitary hormones play a crucial role in puberty, growth, and cognitive development. Changes in the level of these hormones following TBI are likely to negatively affect both short- and long-term outcome in children. Despite increasing awareness and number of publications regarding adults, little to no studies are being completed in children, and there continues to be a significant lack of consensus for testing, timing of evaluation, diagnostic criteria, monitoring, and treatment. To date, there are only five prospective studies that follow pituitary dysfunction in juveniles.[42–46] The evolution of hypopituitarism appears to be similar to adults in that patients presenting with acute deficiencies begin to improve within 6 months, and a subset of children have either chronic deficiencies or develop new deficiencies over time.

Einaudi et al. prospectively studied 30 children at 0, 6, and 12 months after injury. Acutely, incidence of pituitary dysfunction was 23%; at 6 months, the incidence was 4%; and at 12 months, the incidence was 10% with one patient developing GH deficiency.[42] Kaulfers et al. prospectively studied 31 children and adolescents. The incidence of any isolated deficiency was 15% at 1 month after injury, 75% at 6 months, and 29% at 12 months after TBI. Twenty-two

percent of adolescent females had loss of menstrual regularity within the first 6 months after injury, but all resolved by 1 year. Only one patient with GH deficiency of the 13% did not recover by 1 year. Two of 13 children still had persistent thyroid abnormalities at 1 year. Children with diabetes insipidus (DI) (9.7%) and elevated prolactin (33%) all resolved by 12 months. Four of six prepubertal age children developed precocious puberty.[43] Casano-Sancho et al. prospectively followed 37 children for 1 year at 3 and 12 months after TBI. Forty-eight percent had GH deficiency that persisted in 34% of the affected patients, and 43.4% had suboptimal cortisol response, which normalized over time in 70% of patients.[44] Personnier et al. prospectively followed 87 children and adolescents with follow-up endocrine assessment performed between 6 and 18 months after injury. Initial assessment demonstrated GH deficiency in 40% of children. Upon follow-up, in 33 patients who underwent repeat GH testing, 27 continued to demonstrate GH deficiency.[45] Ulutabanca et al. prospectively followed 41 children in the acute phase and 12 months postinjury. Acutely, 44.3% of patients had at least one hormone deficiency, and 17%, 2.4%, and 24.4% were deficient in TSH, FSH/LH, and ACTH, respectively. At 12 months, all acute deficiencies resolved, 9.1% of patients developed GH deficiency, and one patient was deficient in ACTH.[46]

Hormone deficiencies can profoundly impact ongoing brain and physical development and long-term recovery following injury. Due to the nature of "growing into the injury" with children, most children in case reports of hypopituitarism were not diagnosed until years after their injury resulted in issues with growth and/or pubertal development and, in the most severe case, suicide as a result of abnormal development.[47] Unlike adults, if treatment is delayed too long, many of these effects are not reversible as the developmental window for a specific hormone's actions has passed.[48,49] This emphasizes the need to both identify onset of hormonal changes and treatment strategies so that a patient's short- and long-term outcomes can be optimized.

Natural history

The time course of hypopituitarism following TBI is currently understudied. Results from meta–analysis and acute versus chronic studies suggest that a large percentage of patients recover pituitary function over the first few months while another group has chronic deficits. Several prospective longitudinal studies have assessed pituitary function following TBI out to 1 year and have helped to better define the evolution of dysfunction and recovery. These studies generally demonstrate that deficiencies observed at acute time points begin to resolve by 3 months and continue to resolve over the course of a year. Again, GH and gonadotropin were the most commonly affected axes, and gonadotropin deficiencies were the most likely to recover with GH deficiencies being more persistent. In patients with sustained GH deficiencies, this was associated with more severe acute GH deficiency and cortisol hyposecretion. A subset of patients that either had no acute dysfunction or only had an isolated deficiency went on to develop either isolated deficiencies or multiple hormone deficiencies at 6 or 12 months and typically involved ACTH.[50] Three prospective studies have gone on to monitor pituitary function after 1 year. In a 3-year prospective study by Tanriverdi et al., 23.3% had GH deficiency, and 6.6% had ACTH deficiency 3 years after TBI.[51] The same group followed up with a 5-year prospective study in which most of pituitary deficiencies improved over time, but there were significant hormone deficiencies 5 years following injury (28% GH, 4% ACTH, and 4% gonadotropin).[52] In the Kleindienst study, 48% and 39% of patients continued to have ACTH and GH deficiencies 24–36 months postinjury.[53] These data strongly suggest the need for further prospective longitudinal studies as it appears hypopituitarism can evolve over time and present at different time points in different patients. Further work to determine what cohort is at acute versus chronic risk could help guide screening and treatment protocols following TBI.

Sports

Despite TBI being a well-known cause of hypopituitarism, it is currently unknown how repetitive mTBI (RTBI) might be a risk factor for developing pituitary dysfunction. This is of significant interest given the current climate surrounding combative/collision sports. Data regarding the frequency of hypopituitarism due to sports-related brain injury are limited. In adults, there appears to be a cumulative effect between frequency of RTBI and hypopituitarism. In one preliminary study, GH status and insulin-like growth factor-1 (IGF-1) levels were compared between 11 actively competing or retired male amateur boxers and a control group. GH deficiency was found in 45% of the boxers, and in addition, IGF-1 levels were significantly lower in boxers.[54] Tanriverdi et al. compared GH status and IGF-1 levels of 22 amateur kickboxers compared with a control group. IGF-1 was significantly lower in the kickboxers than in the control group; 22.7% had a GH deficiency, and 9.1% had an ACTH deficiency.[55] The same group investigated pituitary function in retired or active amateur boxers. Similarly, they found 15% of boxers deficient in GH and 8% deficient in ACTH. Retired boxers had a higher rate of pituitary dysfunction (47%) compared to active boxers (18%).[56] Kelly et al. investigated pituitary and metabolic function in retired football players and reported that 28% of players were GH deficient. Players with hormone deficiencies had significantly lower QoL, poor metabolic function, and decreased erectile function.[57]

Children, especially adolescents, are also at risk for sports-related injuries. One of the highest risk factors of TBI in adolescents is sports-related injury. According to CDC statistics, 2.6 million children <19 sustain all sports-related injuries of which 250,000 suffer TBI. This number reveals that 50% of all documented TBI cases are sports-related, and adolescent children aged 15–19 are at greatest risk. This group accounts for 1 million sports-related injuries and

60,000 sports-related TBIs of any severity with incidences increasing annually.[25] Although incidence of RTBI is difficult to quantify, it appears that about a third of those within the adolescent range have received multiple concussions.[58] The risk for subsequent TBI increases with the number of previous concussions and with age such that incidence of a second TBI is twofold greater among children 14 years and younger and threefold greater for 15- to 24-year-olds.[59] There is currently only one case study that provides a link between sports-related RTBI and hypopituitarism. Ives et al. reported a case of a 14-year-old soccer player who had experienced four concussions within 4 months. After the fourth injury, the player had stunted growth, decreased athletic ability, and poor energy levels. Upon testing, the patient was found to be deficient in GH, ACTH, and TSH.[60] These findings all suggest that RTBI has a cumulative effect on pituitary dysfunction.

PATHOPHYSIOLOGY OF TBI-INDUCED HYPOPITUITARISM

Anatomy and location of the pituitary

Location and anatomy of the pituitary make it particularly susceptible to injury. The pituitary gland, typically weighing less than 1 gram and measuring approximately 8 mm by 10 mm, is located within the sella turcica in the skull base and is tethered to the hypothalamus by the infundibular stalk.[61] The pituitary gland primarily receives its blood supply from the internal carotid arteries. The long hypophyseal portal vessels, which arise above the diaphragm sella from the superior hypophyseal arteries, travel down the infundibulum to provide the anterior pituitary with 70% to 90% of its blood supply. The short hypophyseal portal vessels arise from the inferior hypophyseal artery, enter the sella from below the diaphragma sellae, and supply the gland with less than 30% of its vascular supply, predominantly in the medial portion.[62–64]

The pathophysiology of TBI-induced hypopituitarism is not completely understood. Although several theories have been proposed, the primary theory involves vascular damage to the pituitary gland. The pituitary is encased in the bony sella and is likely exposed to mechanical trauma at the time of impact. This mechanical force results in shearing and rotational injuries that may damage the vasculature, the pituitary gland itself, the infundibular stalk, or the hypothalamus although damage to the long hypophyseal portal vessels is believed to be the main mechanism. In addition to mechanical forces, secondary insults occurring after the primary injury, such as hypotension, brain swelling, and intracranial hypertension, may further contribute to injury to the pituitary gland.[9,33,64,65] This is supported by early autopsy studies that observed necrotic infarctions within the pituitary and/or hypothalamus in up to one third of fatal head injury patients.[8–11] The pattern of infarction was in the blood supply pattern of the long hypophyseal portal veins, and tissue in the area of the short portal veins survived.[8]

In more recent studies utilizing modern imaging techniques, magnetic resonance imaging was used to monitor pituitary volume as well as observe any pathological changes. The authors found that immediately following injury, the pituitary gland was enlarged compared to controls, and they also found focal abnormalities, including hemorrhage, infarction, signal abnormalities, and/or partial stalk transection. Follow-up scans found that pituitary volume was significantly decreased compared to acute scans and atrophy of the anterior lobe in two patients.[66] Zheng et al. compared changes in the apparent diffusion coefficient (ADC) in 42 TBI patients 1 week postinjury and endocrine evaluation at 1 month postinjury. Those with TBI had a decreasing ADC compared to controls, and TBI patients with pituitary dysfunction were found to have an even significantly lower ADC. The authors were able to correlate the 1-week ADC as a predictive measure of who was hormonally deficit at 1 month postinjury.[67]

In addition to histological and imaging evidence to support a vascular injury theory is the pattern of hormonal loss. The somatotroph (GH) and gonadotroph (LH/FSH) axes are consistently the two most affected by TBI.[13,35,68] The somatotrophs are primarily located in the lateral wings of the anterior pituitary, and the gonadotrophs are scattered throughout the pars distalis and are the major cell group in the pars tuberalis. These are both anatomical areas that are supplied by the long hypophyseal portal vessels, and an infarction in these regions would affect those cell types. This is in contrast to the corticotrophs and the thyrotrophs, which are located in areas supplied by the less susceptible short hypophyseal portal vessels.[69] A recent study by Greco et al. utilized Evans blue extravasation as a measure of vascular permeability within the pituitary and observed that with increasing numbers of mTBIs, vascular permeability of the pituitary also increased.[70]

Inflammation and autoimmunity

The mechanisms responsible for chronic hypopituitarism following TBI are currently unknown. It is not yet understood why a significant amount of patients are able to recover within a year of injury while a population of patients continue to have chronic deficits, worsen over time, or develop new deficiencies. It is well known that abnormal neuroinflammation arises from TBI and is thought to play a significant role in the development of complications and neurodegenerative disease following TBI.[71] Attention has been growing in regards to the generation of central nervous system (CNS) autoantibodies following TBI and may be a partial explanation for chronic pituitary dysfunction.

One theory is based on and complementary to the hypothesis of vascular injury, which results in necrotic cell death within the pituitary gland. The process of necrosis induces the inflammatory pathways in order to contain the injured cells and chronically to support spontaneous brain regenerative processes.[72] One theory is that this stimulates the innate immune system that uses activation of microglia,

macrophages, natural killer cells, and the complement system. In the injured state, this leads to an abnormal state of activation that, in turn, causes excessive release of cytokines, further increasing vascular permeability and release of dead pituitary cells into the systemic and lymphatic systems. This, then, leads to recognition by and overactivation of B cells that begin to produce autoantibodies against the "foreign" pituitary tissue.[73] This chronic "attack" of autoantibodies over time likely overcomes any recovery mechanisms and potentially leads to the chronic pituitary dysfunction observed following TBI.

The involvement of autoantibodies against the pituitary (APA) and hypothalamus (AHA) in the pathogenesis of TBI-induced hypopituitarism was hypothesized by Tanriverdi in 2008. In their first study, 29 patients were examined 3 years postinjury for pituitary function and presence of serum APA compared to controls. APA were detected in 44.8% of TBI patients and none in controls. Risk of pituitary dysfunction was significantly higher in those who were APA positive. Further, there was a significant positive correlation between APA titer and peak GH levels in response to a stimulation test.[74] In their second study, 25 patients from the 2008 study were evaluated at 12 and 60 months postinjury for pituitary function and APA and AHA. At 12 months, 44%, 4%, 8%, and 16% of patients were GH, TSH, FSH/LH, and ACTH deficient, respectively. At 5 years postinjury, 28%, 4%, and 4% of patients were GH, FSH/LH, and ACTH deficient, respectively. In addition, 60% and 48% of patients were AHA and APA positive, respectively. Antibody positivity was only found in those who continued to have hormonal deficits at 5 years postinjury.[52] In their most recent study, pituitary function and APA and AHA were determined in 61 active and retired boxers. AHA and APA were found in 21.3% and 22.9% boxers, respectively, but in none of the controls. Of the 61 boxers, 18% were hormonally deficient, 3.3% were ACTH deficient, and 9.8% were GH deficient. It was also found that 9.8% were AHA positive, and 4.9% were positive for APA. Autoantibody titers were significant higher in boxers with hypopituitarism, and hypopituitarism was significantly associated with AHA but not APA.[56] These studies confirm the existence of autoantibodies against the pituitary gland and hypothalamus but have several limitations, including small sample size and use of a cross-sectional study design. Despite these limitations, it is an area that warrants strong investigation and development of long-term prospective studies in controlled larger cohorts to help define the role of autoimmunity in TBI–induced hypopituitarism.

HORMONES AXES DISRUPTED BY TBI

TBI-induced anterior pituitary dysfunction

GROWTH HORMONE

The production and release of GH is stimulated by GH-releasing hormone (GHRH) and suppressed by GH release-inhibiting factor/somatostatin. GH, in turn, activates IGF-1 to act on target tissues to decrease protein catabolism, mobilize fat, decrease carbohydrate utilization, and increase insulin resistance. One of the caveats in measuring GH is that it has a short half-life in plasma, and its pulsatile secretion varies throughout the day, making single, basal measurements of GH difficult to interpret and compare between patients.[75] IGF-1 has a long half-life, and although it is used to screen for GH excess, it is increasingly being found not to be a sole predictive screening tool for GH deficiency.[76,77] GH is produced and released by somatotrophs within the lateral wings of the pituitary gland. They receive blood supply from the long portal vessels, making them uniquely vulnerable to damage due to vascular injury, stalk injury, anoxia and glucose deprivation.[69] Deficiencies of GH have been associated with poor QoL, impaired executive function, metabolic changes, and negative changes in brain and physical development in children.[78–80]

The variability of GH deficiency following TBI has a large range and may be due in part to the difficulties associated with testing. Some variables include the use of basal versus dynamic testing, type of stimulation test, diagnostic criteria, and normalization to body mass index. Despite the large variability, GH is one of the most commonly disrupted axes following TBI. In a postacute study of 50 subjects, GH and IGF-1 were measured within 20 days of injury. Eighteen percent were observed to have GH deficiencies.[81] In another study, 34 TBI subjects were assessed with GH provocative testing, and GH deficiency was observed in 9%. Other acute studies have shown great variation with no association to GCS or outcome.[82] Wagner et al. showed an acute decrease in GH followed by a decrease and slight normalization of IGF-1 within 10 days of injury.[83] In longer prospective studies, TBI patients showed 3- and 12-month GH deficiency rates of 21% and 20%,[84,85] respectively, in one study and 9% and 10% in another.[86] Lieberman et al. reported GH deficiency in 14.6% of patients at a median of 13 months postinjury; another study reported 7.8% at a median of 17 months and most recently an incidence of 45% in patients more than 1 year from injury.[37]

GONADAL

The two principle gonadatropins are LH and FSH. Gonadatropin-releasing hormone is secreted by the hypothalamus causing release of LH/FSH. LH/FSH then act on their target organs (ovaries and testes) to produce testosterone and estrogen.[87] Their location within the anterior lobe also puts them at risk for vascular damage. As a result, LH and FSH deficits share the highest incidence rates with GH. Stress and injury are known to decrease gonadotropin levels as a compensatory mechanism to slow metabolism, and as such, it may be difficult to determine whether acute decreases are due to the injury or to pituitary damage.[88] This is of clinical significance as both testosterone and estrogen have been shown to be neuroprotective and inflammatory mediators.[89–91] Chronic deficiencies in these areas have been associated with memory and cognitive deficits, sexual dysfunction, and negative changes in muscle mass.[48,92,93]

Low levels of LH/FSH and testosterone/estrogen have been observed within acute time points following injury. In an acute study, low testosterone was present in 82.1% of men at day one and 100% by day four. A similar deficiency was found for days one and four for LH (55.2% and 58.6%) and FSH (10.3% and 37.9%). Conversely, another group of patients showed elevations of day one and four LH (6.9% and 6.9%) and FSH (6.9% and 3.4%).[94] In a cohort of patients examined within 20 days of injury, 79% had low testosterone.[95] Another study that measured testosterone 7 days postinjury showed an incidence rate of 67%.[96] Wagner et al. also reported early suppression of the pituitary-gonadal axis after TBI with low LH in 83%, FSH in 63%, and testosterone in 100% of men and low estradiol in 43% of premenopausal women.[83] Klose et al. reported 68% of patients had hypogonadotropic hypogonadism after acute TBI.[97] In the acute phase, Agha et al. reported gonadotropin deficiency in 80% of patients unrelated to the presence of prolactin.[81] A cross-sectional study that ranged in a postinjury median of 17 months had a prevalence of 11.8%.[35] In a prospective study, central hypogonadism was seen in 17% and 11.4% of patients at 3 and 12 months, respectively.[84,85] Similar results were seen by Schneider et al., who observed deficiencies in 32% and 21% at 3 and 12 months, respectively, confirming a tendency of patients to improve over time.[86]

ADRENAL

One of the most clinically relevant axes to be disrupted is the hypothalamic-pituitary-adrenal (HPA) axis. Corticotropin-releasing hormone (CRH) from hypothalamic neurons activates ACTH in the pituitary, which then acts on the adrenal glands to induce the release of mineralcorticoids, glucocorticoids (cortisol), and adrenal precursor hormone, dehydroepiandrostenedione (DHEA). These have a central role in regulating many homeostatic systems within the body, including metabolism, the cardiovascular system, and the central nervous system. Normally, cortisol rises in times of stress to maintain blood pressure and increase glucose availability.[98] Following TBI, excessive activation and deficiency of the HPA axis have been observed.

Corticotropin insufficiency can lead to adrenal insufficiency, leading to hypotension, hyponatremia, and hypoglycemia, and may be life-threatening.[99] Serum cortisol levels can vary according to severity and time after injury. Some studies have shown an immediate increase followed by a slow decrease back to baseline during recovery, and others have shown normal plasma levels but increased free cortisol.[100,101] However, the majority of studies have shown acute decreases followed by improvement and full resolution within 12 months. Acute studies have shown deficits of up to 16% and 24%,[81,82] and chronic studies at 1 year only show deficits in 6.4% individuals and, at 64 months postinjury, 7.4% of patients.[36] One study found that in mild-to-moderate TBI, normalized plasma cortisol was predictive of a positive outcome;[102] others have found that acute ACTH deficiency is predictive of chronic GH and gonadotropin deficiency.[81] Overall, pooled incidence of ACTH deficiency ranges from 4% to 53%.[103,104]

THYROID

Injury to the thyrotropes is less common than other areas of the pituitary due to their central location within the anterior lobe, and therefore, pituitary-thyroid axis disruption is not as commonly observed as other hormones. Thyrotropin-releasing hormone released from the hypothalamus activates TSH secretion from the pituitary gland and, subsequently, regulates the release of T3 and T4 from the thyroid. T3 and T4 are primarily responsible for regulating basal metabolic rate, protein synthesis, neuronal maturation, and cell differentiation.[105] Assessment of thyroid hormone is difficult to assess during acute phases following TBI, as both T3 and T4 naturally decrease during stress and illness.[106] Parsing out whether deficiencies are due to pituitary damage or the stress of the injury become difficult. Central thyroid dysfunction is rare following TBI, and it is now recommended to wait until a later phase in recovery to make any assessments.

Acutely, within the first month of injury, only one of 50 patients was found to have secondary hypothyroidism.[33] In the following chronic study, at a median test time of 13 months, 21.7%, 10%, and 2.9% of patients were deficient in TSH, T4, or both, respectively.[37] In one prospective study examining 100 patients at 12 months postinjury, secondary hypothyroidism was diagnosed in 5% of patients.[85] Schneider et al. prospectively followed 78 patients at 3 and 12 months postinjury and found 8% and 3% of patients diagnosed with secondary hypothyroidism, respectively.[86] Similar to other hormonal axes, the majority of cases resolved within 1 year's time.

PROLACTIN

Primarily, pituitary prolactin secretion is regulated by hypothalamic dopamine neurons and is synthesized and released by lactotroph cells, but it is also regulated by TSH. Although it is best known for its function in stimulating lactation, it plays a significant role in immune system modulation and can act in a cytokine-like manner. In addition, high levels of prolactin modulate hormone systems, namely, the gonadotropin axis. In the presence of high prolactin, gonadotropin-releasing hormone (GnRH) is reduced, and subsequently, both testosterone and estrogen production decline.[107] Following injury, compression and/or injury to the infundibular stalk is thought to be the cause of observed hyperprolactinemia although studies overall are variable in their report findings.[108]

In one hyperacute setting, severe TBI patients showed elevated prolactin on days one and four in 67% and 77% of patients, respectively. No associations were found with increased mortality, outcome, or Glasgow Coma Scale (GCS) score.[109] In contrast, an acute study that observed 52% incidence of hyperprolactinemia found a negative correlation between prolactin levels and GCS.[35] Two similar prospective studies following patients at 3 and 12 months

postinjury found an incidence rate of 4.2% and 5.7% in one study[84,85,110] and 3% and 4% in the other, respectively.[86] In the study in which acute hyperprolactinemia was associated with GCS, the majority of patients recovered by 6 months, and only 13% remained hyperprolactinemic at 1 year[50] similar to Kelly et al., who found 26% of patients with elevated prolactin at a median 26 months postinjury, although other studies show little to no incidence of chronic prolactin elevation.[33]

TBI-induced posterior pituitary dysfunction

ANTIDIURETIC HORMONE

Antidiuretic hormone's (vasopressin) two main primary functions are to retain water in the body and to constrict blood vessels. Vasopressin regulates the body's retention of water, acting to increase water reabsorption in the kidney's collecting ducts. It also increases peripheral vascular resistance, which, in turn, increases arterial blood pressure. It also has a homeostatic role in the regulation of water, salts, and glucose within the blood. It is synthesized within the hypothalamus and stored within the posterior pituitary. The main stimulus for secretion of vasopressin is increased osmolality of the blood.[111] Injury or dysfunction of the posterior pituitary is more clinically apparent than anterior pituitary dysfunction.

Diabetes insipidus (DI) is a well-known complication of TBI and is associated with more severe head injuries and a higher mortality rate.[112] Timely diagnosis and treatment are important as uncontrolled DI can lead to hypernatremia in which mortality is then increased. Acutely, at a median of 12 days postinjury, 26% of TBI patients had DI.[35] Aimaretti et al. reported, in a prospective study, DI in 4.2% and 2.8% of patients at 3 and 12 months, respectively.[84,85] Chronically, DI was also reported in 14% of 50 TBI patients studied between 12 and 64 months postinjury.[36] In another chronic study at 12 months postinjury, it was determined that only 12% of patients with acute DI had persistent deficits.[50] In other studies, DI was reported to be 21.2% acutely and 7% at a median of 17 months.[113]

CLINICAL MANIFESTATION OF TBI-INDUCED HYPOPITUITARISM

The recent studies over the past 15 years have demonstrated that TBI-induced hypopituitarism occurs at a much higher rate than was previously thought. What is still not fully understood is how it may potentially contribute to the morbidity and mortality associated with TBI. Pituitary dysfunction is now known to affect neuropsychiatric outcome, QoL, body composition, executive function, memory, and cognition. Patients present with nonspecific symptoms, such as fatigue, weakness, cold intolerance, decreased appetite, weight loss/gain, headaches, abdominal pain, low blood pressure, visual disturbances, menstrual irregularities, and sexual dysfunction. Because the subtle symptoms due to hypopituitarism could result from different causes, most patients with hypopituitarism remain undiagnosed and, thereby, untreated. With improving awareness of the incidence of TBI-induced hypopituitarism, it is becoming indisputable that pituitary function assessment be incorporated into the care of TBI patients.

Impairments in neurocognition

Cognitive dysfunction observed after TBI is not only due to the injury itself, but hypopituitarism may play a significant role. GH deficiency in TBI patients has been associated with deficits in attention, executive functioning, and memory. Low peak GH levels after provocative testing were also a strong independent predictor of poor rehabilitation outcomes as determined by measures of cognition and functional independence and has been associated with impairments of memory and verbal learning. Low testosterone has also been associated with poor cognitive outcome at 6 and 12 months postinjury, including impairments of verbal fluency, visual and verbal memory, and visuospatial processing.[114]

Bondanelli et al. studied 72 patients in postinjury rehabilitation. Peak GH response correlated to the Functional Independence Measure and Level of Cognitive Functioning Scale at discharge and negatively with the Disability Rating Score at discharge. Unfavorable outcome measures occurred in patients with hypopituitarism as compared with normal pituitary function. Multiple regression analysis identified both GCS and GH peak as strong independent predictors of outcome.[68] León-Carrión et al. compared neuropsychological assessment and hormonal evaluation 6 months after TBI diagnosis between TBI patients with and without hormone deficits. Those patients with GH deficiency show greater deficits in attention, executive functioning, memory, and emotion than those without.[115] Kozlowski-Moreau et al. evaluated 55 patients with persistent cognitive and/or behavioral disorders at least 1 year postinjury. GH deficiency was associated with attention and verbal memory disorders and reduced involvement in activities of daily life.[116] Ioachimescu et al. found that GH deficiency has adverse effects on executive abilities and mood in male veterans with mTBI.[117]

Neuropsychiatric disability and QoL

Neuropsychiatric disturbances following TBI occur irrespective of severity and are often persistent. These problems should be promptly diagnosed and treated as they can significantly interfere with recovery and rehabilitation as well as with QoL. Symptoms can include anxiety, agitation, and irritability, and it is often difficult to discern whether these are symptoms of depression or of other comorbid entities. Changes in mood, body appearance, or libido can all contribute to poor QoL and increase depressive symptoms.

Studies have found associations between TBI-induced hypopituitarism and an increased amount of severity of

neuropsychiatric symptoms in patients. Several groups have found a lower QoL score in hormone-deficient patients. Nourollahi et al. compared TBI patients with and without pituitary dysfunction and found lower scores in those with deficiencies.[118] Kelly et al. had similar findings in a study assessing 44 TBI patients 6–9 months postinjury for reduced QoL and neurobehavioral deficits. GH deficiency was associated with higher rates of at least one marker of depression and reduced QoL, specifically impairments in energy and emotional well-being, compared with patients with TBI without GH deficiency.[119] Kreber et al. also showed higher levels of depression and disability and lesser ability to perform activities of daily living and initiate tasks in severe GH-deficient patients at least 1 year postinjury.[76] Popovic et al. found an overall increase in depressive scores in the TBI group and a specific negative correlation between peak GH and paranoid ideation and somatization.[114] A prospective study from 2015 showed association between low testosterone global outcome, disability, and cognition at both 6 and 12 months postinjury.[120] Interestingly, in Maric et al., a small cohort of patients were given a baseline test for psychiatric and cognitive functions followed by GH replacement for 6 months, retesting, removal from treatment for 12 months, and another retest. Six months of GH therapy in GH-deficient TBI patients improved cognitive abilities and significantly improved psychiatric functioning. Severity of depression decreased as well as intensity of interpersonal sensitivity, hostility, paranoid ideation, anxiety, and psychoticism. Somatization, obsessive-compulsive symptoms, and phobic anxiety decreased in all except one patient. In three GHD subjects who stopped GH therapy for 12 months, the investigators observed worsening of the verbal and nonverbal memory as well as symptoms of interpersonal sensitivity, anxiety, and paranoid ideation.[121] Although these studies do not prove a causal relationship between TBI-induced hypopituitarism and neuropsychiatric disorders, there is strong evidence that there is a link between the two, and this warrants further investigation into hormonal supplementation.

Physical appearance and sexual health

In adults, GH deficiency causes impaired cardiac function, decreased exercise tolerance, reduced lean body mass, central body fat distribution,[122] and reduced bone mineral density, which may be of particular significance in immobilized and elderly patients.[123] Prodam et al. showed that TBI patients with pituitary dysfunction had a worse metabolic profile that included insulin resistance, altered glucose levels, and dyslipidemia compared to TBI with normal hormonal values.[124]

In addition to GH, changes in sex steroids can have profound affects on the body. Prolonged hypogonadism can lead to gynecomastia, diminished facial and body hair, and small and soft testicles.[125] Testosterone deficiency in males is associated with reduced lean body mass, muscle weakness, erectile dysfunction, and impaired exercise tolerance.[126] In both males and females, sex steroid deficiency results in reduced bone mineral density and osteoporosis.[127] Although not closely attended to, hyperprolactinemia may be an additional cause of hypogonadism due to the effect of raised prolactin levels on normal pulsatile gonadotropin secretion.

Beyond physical attributes, changes in GH and sex steroids can affect sexual health and function, and this is of significance as patients have expressed having a satisfying sexual life contributes to their overall QoL. Often, many of the symptoms that an individual with TBI experiences (e.g., impairments in motor, sensory, cognitive, behavioral, and emotional functioning) can affect a person's sexuality in different ways. Thirty percent of TBI patients expressed dissatisfaction with their sexual life,[128] and between 4% and 71% of adults complain of actual sexual dysfunctions.[129–131] Despite gonadotropin deficiency having one of the highest incidence rates, there is currently only one clinical study that links TBI-induced hypopituitarism with sexual function. Kelly et al. showed that International Index of Erectile Function (IIEF) scores were significantly lower in TBI patients with hypogonadism versus those without.[57] Sexual health and function is an often-ignored issue following TBI, and both patients and health care professionals have expressed that they are embarrassed or uncomfortable to bring up the topic and want to wait for the other person to discuss it first.[132]

Adolescent development

In childhood and adolescence, GH deficiency impairments in linear growth and development are a common finding and has been proposed to be used as a clinical indication of pituitary dysfunction; however, not all children with GH deficiency have short stature. Beyond physical and pubertal developments observed during adolescence, it is also a period of critical anatomical and functional changes in the brain. Remodeling of cortical and limbic circuitry result in maturation of reproductive, cognitive, social, and emotional axes necessary for proper function during adulthood. Activity of neuroendocrine axes, including GH, gonadal, and HPA peak during adolescence, influence neuronal plasticity and gene expression, resulting in permanent organizational changes within the brain.[23,24] Disruption of critical developmental processes during adolescence results in long-term disability throughout adulthood. Causation between isolated hormone deficiencies during childhood or adolescence and perturbed adult function has been shown in several syndromes[22,30,98,133] and underscores the importance of proper endocrine function during adolescence. Despite growing evidence showing a clear relationship between TBI and hypopituitarism in children, few studies specifically address recovery and development. Only two studies have specifically analyzed QoL scores and neuropsychological testing with both showing hormone deficiencies and poor QoL in children.[134,135]

TBI-INDUCED HYPOPITUITARISM: HOW TO TEST?

Patient screening for pituitary dysfunction

The first consensus guideline on screening for hypopituitarism following TBI was published by Ghigo et al. in 2005.[77] In this guideline, it was suggested that all moderate-to-severe patients should have baseline evaluation for hormones during the acute phase followed by prospective evaluations for 12 months.[77] Agha and Thompson followed this in 2006 to include that patients with mild injuries should be screened if clinically indicated.[136] The caveat in these initial guidelines is that they are based on a limited amount of studies and assume pituitary dysfunction prevalence is based on severity of injury. However, recent work from Schneider et al. has shown that, although incidence of hypopituitarism is highest in severe TBI, the rates are still high in both mild and moderate cases (16.8% mild, 10.9% moderate, and 35.3% severe). Their recommendation was to screen all patients who were admitted to the hospital.[21] Again this assumes those with mTBI are not experiencing pituitary dysfunction despite that fact that the incidence rate is substantial, and significantly more mTBIs occur than severe TBI.

It is neither practical nor fiscally responsible to expect to screen every mTBI patient. So how do you select who will be screened without any predictive factors? It has, therefore, been proposed that, among patients of all trauma severities, only those who are symptomatic of hypopituitarism, have been hospitalized, or display predictive radiologic findings as previously discussed should undergo screening. Recently, Tanriverdi et al. have suggested stratifying the mTBI group into complicated versus uncomplicated.[137] Their rationale for this is that the mTBIs that compromised the pooled risk in the 2011 Schneider et al. meta-analysis were actually almost all complicated mTBI. They further address the heterogeneity of the mTBI population, stating, "It is documented that approximately 40% of mild TBI patients do not experience loss of consciousness. However, previous studies have shown that approximately 10%–39% of patients with mild TBI have intracranial abnormalities (e.g., hematoma, edema, or contusion) detected on computed tomography (CT) on the day of injury" (p. 1837).[137] This is further justified by data from van der Eerden et al., by which they screened all emergency department patients for pituitary dysfunction and found a very low rate of dysfunction[138] compared to another study from the Tanriverdi group that monitored pituitary dysfunction only in those who needed hospitalization for more than 24 hours.[51] Based on all of this, these authors recommend screening only moderate, severe, and complicated mTBI cases that require more than a 24-hour hospital stay. Any mTBI with no loss of consciousness and/or posttraumatic amnesia for less than 30 minutes would be excluded from testing. They suggest this would exclude more than 50% of unnecessary testing.

Timing of testing for pituitary dysfunction

The natural history of TBI-induced hypopituitarism is dynamic. Deficits that present immediately after injury appear to resolve or persist or new deficits begin to develop over time, making it difficult to determine when to test for pituitary dysfunction. In addition, hormonal changes during the acute phase may actually be related to a stress response from the injury and not damage to the pituitary. There is also no documented correlation between acute hormone dysfunction and prediction of chronic deficits. It does not, then, the consensus of several, appear that basal or dynamic testing during the acute (10–14 days postinjury) period is useful to the patient, and there are no studies showing any benefit of early treatment of GH, LH/FSH, and TSH. In contrast, any patient with life-threatening signs or symptoms of hypopituitarism, such as adrenal insufficiency or DI, should be immediately tested for these deficiencies as they are life-threatening, and current evidence shows perturbed HPA axis function is associated with worse outcome and may lead to increased risk for morbidity and mortality.[77] It is, then, the consensus of several authors that initial testing should only be focused on adrenal insufficiency.

Controversy also begins to arise over when to begin testing for hormone dysfunction during the chronic phase. In most cases, pituitary dysfunction appears to resolve within 3–6 months. Some authors argue for early clinical evaluation between 3 and 6 months postinjury followed by testing, if necessary.[136] Others state that because most cases are resolved by 6 months, no testing is needed until 6 months, at which time, hormones should be tested and subsequently followed up 6 months later, if there are any present deficiencies.[139] Other groups do not believe any testing should take place until 12 months postinjury as all hormones are usually recovered by then, and they do not think supplementation with any hormones during that period would be helpful to rehabilitation and recovery.[137] For patients who still have deficiencies at 1 year postinjury, further follow-up is recommended. Unfortunately, there is a paucity of long-term data regarding the time course of hypopituitarism resolution. There are currently only three studies that observe patients past 1 year postinjury, and in these studies, a significant portion are still GH- and ACTH-deficient.[51–53] Continuation of these kinds of studies will improve our understanding as to how long after the initial injury hypopituitarism can develop or resolve.

TBI-INDUCED HYPOPITUITARISM: WHEN TO TREAT?

Current hormone replacement therapy (HRT) recommendations are based on the 2005 recommendations by Ghigo et al.[77] In this publication, HRT is generally recommended to wait a year before beginning treatment. This is based on the evolving nature of hormone recovery and that most deficiencies resolve by 12 months and, therefore, do not require supplementation. The authors suggest that patients

be screened at 6 months and tested and treated as needed on a case-by-case basis. Their general recommendations for treatment under 12 months recommend, in the case of panhypopituitarism, that all hormones be treated immediately except GH. If GH does not resolve, supplementation may be needed. In multiple hormone deficiencies, a similar protocol is recommended. In the case of isolated deficiencies and DI, secondary adrenal insufficiency and secondary hypothyroidism should be treated immediately, gonadotropins as appropriate, and GH on a case-by-case basis. Although the recommendations have not changed since publication, Tanriverdi et al. have made additional suggestions regarding longer time points after injury and have recommended longer surveillance, if necessary.[137] At the time of publication of the Ghigo paper, there were no studies documenting hypopituitarism past 1 year postinjury. Since then, there are now three that show continued GH and ACTH deficits at 3 and 5 years postinjury. More prospective longitudinal long-term studies are needed to define the exact time course of symptom resolution.

The main goal of the treatment of TBI-induced hypopituitarism is to appropriately replace the hormones that are deficient. Although there are currently no class I studies observing HRT following TBI, there are a handful of studies that observe the effects of HRT on patient outcome and recovery. The majority of these studies deal with GH replacement as that is the most commonly affected hormone following TBI. In the 2008 German KIMS database study, 84 TBI patients were compared to 84 patients with nonfunctioning pituitary adenoma (NFPA). GH improved QoL in both groups, but it also improved metabolic abnormalities within the TBI group.[140] Similarly, Gardener et al. reported that baseline QoL was worse in TBI versus NFPA patients, and improvement of QoL by HRT was greater in TBI patients.[141] Maric et al. showed in a very small cohort the reversible nature of hormone deficiency symptomatology. Six subjects who were more than 3 years postinjury had baseline testing done, were placed on HRT for 6 months and tested again. Three subjects stopped treatment and were evaluated 12 months later. Six months of GH therapy in GH-deficient subjects improved cognitive abilities and significantly improved psychiatric functioning. Severity of depression decreased as well as intensity of interpersonal sensitivity, hostility, paranoid ideation, anxiety, and psychoticism. Somatization, obsessive-compulsive symptoms, and phobic anxiety decreased in all except in one patient. In the three GH-deficient subjects who stopped GH therapy for 12 months, the investigators observed worsening of verbal and nonverbal memory as well as symptoms in three symptom checklist dimensions: interpersonal sensitivity, anxiety, and paranoid ideation.[121]

The first chronic study was published as a randomized trial in which subjects were put on GH replacement or placebo. Treatment with GH for 1 year improved the Dominant Hand Finger Tapping Test, Wechsler Adult Intelligence Scale III–Information Processing Speed Index, California Verbal Learning Test II, and the Wisconsin Card Sorting Test (executive functioning).[142] Another small group was given GH or placebo for 3 months, and it was found that controls achieved significant improvements only in digits and manipulative intelligence quotient. GH-deficient patients achieved significant improvements in more cognitive parameters: understanding, digits, numbers and incomplete figures and similarities, vocabulary, verbal IQ, manipulative IQ, and total IQ. GH-deficient patients also reached significantly greater improvements than controls in similarities and in vocabulary, verbal IQ, and total IQ.[143] These improvements in QoL and neurocognition appear to improve outcomes in the observed patients; however, many of the studies have several limitations. Further studies need to be completed to determine the exact impact that HRT has on the rehabilitation and outcome of patients with TBI-induced hypopituitarism.

TBI-INDUCED HYPOPITUITARISM: CURRENT BASIC RESEARCH

As more attention is being paid to TBI-induced hypopituitarism, there is increasing interest in understanding the mechanisms behind how TBI results in hypopituitarism, long-term consequences of hypopituitarism, and how hormonal supplementation may affect brain recovery and behavioral outcome. To date, there are few basic research publications dealing with the aforementioned questions, and this remains an under-recognized area. The earliest publication found was from 2008. The authors were interested in whether expression of hormones (GH, PRL, and ACTH) was elevated in the cortex following TBI similar to ischemia. No changes in hormones were found in the cortex after injury.[144] Negative outcomes associated with exercise in the acute phase following TBI interested Griesbach et al. in comparing stress responses between sham and TBI rats. In the acute phase up to 14 days, they found that restraint stress following TBI led to higher levels of ACTH and CORT compared to sham animals and proposed that injury causes an increased sensitivity to stressful events.[145] This was followed by a 2014 study in which the same group compared forced versus voluntary exercise in TBI and sham animals 1 month postinjury. In postacute phases, exercise does not increase brain-derived neurotrophic factor (BDNF). The authors found that voluntary exercise increased BDNF, forced exercise did not. The forced exercise TBI animals also had higher activation of their corticotropin axis and higher core body temperatures. This data suggested that potent stressors facilitate responsiveness to environmental stimulation.[146]

Several publications have focused on the effects of TBI on pituitary function. Kasturi and Stein performed a bilateral frontal controlled cortical impact (CCI) on adult rats and 2 months later monitored inflammation and pituitary function. They found pronounced inflammation within the pituitary, hypothalamus, and cortex. There was also a significant decrease in both pituitary and serum GH and was the first rodent study to model TBI-induced hypopituitarism.[147]

A study in 2010 looked at the local paracrine response of IGF-1 to TBI. Following CCI, IGF-1 increased in cortical homogenates at 1 hour, and expression was upregulated in pericontusional areas for 48 hours. There was a later increase in the IGF-1 receptor, total AKT, and pAKT. The authors concluded that this might be an early mechanism by which IGF-1 signaling is induced in response to injury in an attempt at endogenous recovery or repair.[148] This was followed by another IGF-1 study in which neonatal rats were injured. Hippocampal cell number was quantified, serum IGF-1 was quantified up to 1 week, and Morris water maze (MWM) was performed to test spatial memory. IGF-1 was significantly reduced at early and late time points and correlated with both significant neuronal loss and poor MWM performance.[149] Greco et al. utilized an adolescent rat injury model to observe effects of GH deficiency on puberty in rats. Animals were given sham, one, or four mTBI (4TBI) injuries (spaced 24 hours apart). The authors found that GH and IGF-1 were significantly reduced in 4TBI compared to sham and single injury animals at 1 week postinjury until 1 month. 4TBI animals were also significantly smaller in both length and weight. Evans Blue dye extravasation was used as a marker of vascular permeability, and they found that with increasing injuries, permeability of the pituitary gland increased.[70] In contrast, Osterstock et al. did not show any injury or increased vascular permeability in their CCI model in mice. They did, however, demonstrate increased inflammation within the hypothalamus and loss of tight junction proteins in the third ventricle. Despite a significant decrease in serum GH, there were no changes in number or function of GHRH neurons within the hypothalamus. The authors concluded that increased permeability of the third ventricle might interfere with communication between the hypothalamus and pituitary.[150] From a more developmental aspect, Greco et al. used the same adolescent RTBI model to examine organization versus activation effects of hormones after TBI. Testosterone was significantly reduced 24 hours after injury up to 1 month after injury, normalized by 2 months, and was correlated to a delay in pubertal onset. Erectile function and reproductive behaviors and reproductive organ growth were significantly impaired at 1 and 2 months postinjury. The authors concluded that the impact of undiagnosed hypopituitarism following RTBI in adolescence has significance not only for growth and puberty, but also for brain development and neurobehavioral function as adults.[151]

Interest in hormones has not only been from an injury and developmental stance, but also for neuroprotection and recovery. Hormones have been shown to be positive modulators of neuronal survival in several injury types. To determine the effect of IGF-1 on neuronal survival, Carlson et al. utilized an IGF-1 overexpressing CCI mouse model. Ten days after injury, they found that, although the amount of neuronal loss was the same compared to wild-type animals, immature neuron density was increased within the subgranular zone. In wild-type injured mice compared to sham for IGF-1 overexpression, neuronal dendrites were shorter and had fewer branches.[152] Another group used a similar IGF-1 overexpressing CCI model. They found there was greater astrocytosis and GFAP within the hippocampus compared to sham and wild-type animals. At 1 and 3 days postinjury, there was a significant decrease in neuronal cell death, and they also observed improved motor and cognitive function.[153] Baykara et al. were interested in observing the anxiolytic and neuroprotective properties of progesterone. They used a neonatal rat CCI model and found that 2–3 weeks postinjury, progesterone improved elevated plus maze performance and rescued TBI-induced decreases in IGF-1 and increases in corticosterone. Progesterone also reduced cell loss within the hippocampus, amygdala, and prefrontal cortex. They also found negative correlations between serum corticosterone and anxiety and a positive correlation between serum IGF-1 and anxiety. They concluded that a single dose of progesterone may be effective in treating anxiety following TBI.[154]

SUMMARY

Acute and chronic pituitary dysfunction is common after moderate and severe TBI and is now being increasingly observed in instances of mild TBI. This hormonal dysfunction can impact early and late recovery processes, ultimately affecting long-term outcome and QoL. The data in the current literature clearly demonstrate that TBI-induced hypopituitarism is a frequent and unresolved problem. More long-term prospective studies in larger numbers of patients are needed to be able to develop an evidence-based screening strategy to make sure all the appropriate patients of all injury severities are screened for pituitary dysfunction. More basic research studies are needed to better understand the pathogenesis and molecular mechanisms that underlie TBI-induced hypopituitarism.

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18

Increasing physiologic readiness to improve functional independence following neurotrauma

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INTRODUCTION

Brain injury rehabilitation prior to the 1980s emphasized the restorative properties of systematic, graded exercise overseen by physical, occupational, and speech-language therapists in inpatient hospital settings. In the early 1980s,[1] the use of centrally acting pharmacologic agents to facilitate inpatient neurorecovery was proposed. This approach was based upon collateral studies in populations other than those with brain injuries and the recognized neurotransmitter actions of these drugs. Over the past 30 years, more specific studies exist regarding the efficacy of dopamine facilitators, SSRIs, and psychostimulants in improving both short- and long-term outcomes after brain injury. Coadministration of methylphenidate to enhance neural recovery became a well-established pharmacologic adjunct in acute inpatient rehabilitation.[2] A comprehensive review of pharmacotherapy in traumatic brain injury (TBI) published in 2014 by Diaz-Arastia et al. provides a current overview of these concepts and the need for future studies.[3]

A logical extension of this concept is employing pharmacologic interventions to enhance and facilitate community participation and productive activity patterns in patients who have sustained neurotrauma. The use of such medications to "correct" neurobehavioral dysfunction has long been recognized as an effective intervention; however, what follows is a systematic methodology to maximize long-term engagement potential while minimizing behavioral avoidance. Instead of emphasizing medication for suppression of disruptive behavior, this chapter defines methods for optimizing neuroplasticity and the prevention of anticipated functional deterioration with aging. Strategies described arise from the limited existing medical literature and descriptive analysis of a cohort of patients from a longitudinal convenience sample derived from an outpatient neurorehabilitation program over 22 years.[4]

BASIC FOUNDATIONS

Conceptually, the neurophysiological basis of rehabilitation represents a learning paradigm not dissimilar in nature to that commonly seen in normal human neurodevelopment and learning (i.e., experience-dependent plasticity). Although it is well recognized that an elementary school student who is sleep deprived, nutritionally challenged, or otherwise lacking in physiologic stability performs at a reduced level, the translation of these principles to the rehabilitation setting is often overlooked. In settings in which funding sources are imposing severe limitations on length of stay and opportunities for intensive rehabilitation, it is especially incumbent upon the treatment team to effectively and promptly address the foundational requirements for optimal learning in rehabilitation.

Consistency and stability of sleep, nutrition, analgesia, hydration, and exercise become prerequisites to maximize

the success of rehabilitation interventions, including the use of pharmacologic agents. Tolerance for preinjury challenges in any of these areas is buffered by the inherent cerebral reserve enjoyed by most healthy individuals. Following neurotrauma, intrinsic homeostatic stability is reduced as demonstrated by enhanced reactivity to smaller perturbations in the internal or external environment. Targeted intervention facilitates the re-establishment of homeostasis to allow subsequent rehabilitation efforts to achieve a higher degree of success.

Sleep

Inefficient or insufficient sleep results in neurocognitive abnormalities, including impaired working memory, impaired phasic attention, and reduced speed of information processing[5] as has been noted in shift workers and medical house staff. Studies of experience-dependent plasticity implicate enhancement of slow wave activity (SWA) during subsequent sleep-to-waking synaptic potentiation.[6,7] Accordingly, "system consolidation"[8] represents sleep-dependent reorganization and distribution of newly acquired information among brain systems. Studies further demonstrate separate roles for slow wave sleep and REM in consolidation of different memory tasks.[9]

Base rates for insomnia in adults are estimated to be 6% in the United States when structured diagnostic criteria are utilized.[10] Preinjury sleep disorders, including sleep-related laryngospasm, obstructive sleep apnea, and periodic leg movements, must be considered whenever a history of nonrestorative sleep is obtained after neurotrauma. Detailed information regarding sleep hygiene and peri-bedtime activities will assist in developing cognitive behavioral intervention strategies. Screening instruments, such as the Epworth Sleepiness Scale[11] and the Sleep and Concussion Questionnaire,[12] provide preliminary diagnostic direction for the clinician and identify those patients who require overnight pulse oximetry to detect nocturnal desaturations that would mandate polysomnographic examination.[13]

Neurotrauma is a cause of sleep-wake cycle disturbance and sleep inefficiency.[14] Investigation of sleep and stroke recovery in humans demonstrates a selective augmentation whereby sleep stability facilitates sequential motor learning and performance.[15] Conversely, adverse effects of sleep disorganization on ADL functioning post-TBI has been well characterized.[16] Infrequently, centrally mediated brain stem injury underlies some disorders;[17] however, weight gain,[18] posttraumatic neuroendocrine deficiencies,[19] and posttraumatic stress disorder (PTSD)-associated hyperarousal states[20] more often combine to disrupt sleep architecture. Myofascial pain syndromes, resolving orthopedic injuries and polytrauma also contribute to sleep disruption. A multidimensional approach to sleep management involving cognitive behavioral therapy, sleep hygiene education, and the selective use of medications or supplements optimizes restorative sleep.[21]

Sleep deficiency is well recognized to increase neuronal irritability and, as such, is employed in sleep-deprived EEGs to enhance the yield of dysrhythmia and seizure events. Studies of hippocampal atrophy as a consequence of nonconvulsive seizures following acute trauma demonstrate the vulnerability of the posttraumatic hippocampus to these events either via neuromodulatory influences of excitatory amino acids or due to heightened metabolic load associated with seizure activity.[22] As any level of neurotrauma increases the potential for seizures across the lifespan, minimizing sleep deprivation or inefficiency becomes a critical component of neuronal homeostasis.

When present, comorbid PTSD results in nocturnal autonomic arousal and requires specific intervention to reduce hyperarousal-induced sleep disruption. Prazosin (a peripheral alpha$_1$ adrenergic antagonist) at bedtime reduces nocturnal arousals due to increased autonomic discharge.[23] Additional strategies for sleep facilitation include the use of magnesium, zinc, melatonin,[24] trazodone,[25] mirtazepine, amitriptyline, doxepin, or quetiapine.[26] Melatonin is commonly given at bedtime in doses of 1–5 mg; however, the use of 0.3 mg given orally 5–6 hours prior to the desired time of sleep onset provides the brain with a more physiologic trigger of neurochemical cascade involved in sleep initiation and maintenance.

Nutrition

Extreme malnourishment, whether generalized or protein in nature, has a recognized impact on the experience-related neuroplasticity of children.[27] As protein synthesis and neuroplasticity are known components of learning (memory acquisition and access), interference with the availability of nutrients produces the well-described syndromes of marasmus and kwashiorkor in children. Although recent studies confirm the potential of alternative pathways for neuronal mitochondrial energy production, the availability of a steady source of glucose (as well as oxygen) is essential to normal brain metabolism.

As experience-dependent neuroplasticity is the basis for normal brain development in humans and also mediates recovery of function following neurotrauma, the critical nature of nutritional stability is self-evident. Clifton and colleagues identified the hypermetabolic state that arises following severe neurotrauma in which rates increase to 150% of baseline.[28] For those of us involved in the clinical management of neurotrauma patients in the early 1980s, the first 3–4 months of inpatient rehabilitation care were devoted to aggressively stabilizing this acute catabolic state before any significant neurorehabilitation endeavors could be initiated.

Nutritional stability becomes the second component of prepharmacologic intervention following neurotrauma. Although the healthy brain demonstrates significant tolerance of vitamin deficiency, caloric instability, and relative hypoglycemia, postinjury loss of cerebral reserve, the development of hypermetabolic states, and ensuing

spreading cerebral metabolic depression coalesce to create an environment in which even mild deficiencies create a more significant potential for disrupting neuroplasticity and recovery.

When neurological evaluation defines deficits in distal vibratory sensation, proprioception or depression, baseline assessments of vitamin B_{12}, vitamin D, and folic acid are indicated to optimize these as potential confounders of neurorecovery. Recent trends in the management of concussive injury has supported the use of omega$_3$ fatty acids (O3FA) to provide substrate for neuroplasticity and repair.[29] Animal studies using a controlled cortical impact rodent model of neurotrauma identify increased susceptibility to TBI and impaired recovery following injury in those subjects with severe depletion of membrane docosahexaenoic acid (DHA).[30] Although longitudinal population-based studies of the use of O3FA in cardiovascular treatment has noted a significant increase in prostate cancer risk with their use in men,[31] further studies are needed to define threshold effects and comorbidity issues before abandoning this intervention. Until then, ongoing clinical vigilance and prostate monitoring is prudent when O3FAs are utilized.

Declines in neurocognitive efficiency observed in normals with hypoglycemia as well as the clinical observation of reduced functioning before meals in those after neurotrauma support the advice of ingesting multiple small meals per day while avoiding high-glucose loads in favor of low glycemic index or even ketogenic diets. Ingestion of caffeine or other stimulants may transiently reduce fatigue or inattention; however, diuretic effects of methylxanthines may worsen hydration status, increase irritability, and lower seizure threshold.[32]

Nutraceuticals have been used to augment or stabilize cognitive functioning in degenerative disorders.[33] Laboratory assessment and replenishment of vitamin D,[34] vitamin B_{12},[35] and folic acid[36] as indicated provides those cofactors essential for neurotransmitter functioning and production. As use of anticonvulsants and antidepressants may result in excessive metabolic need for tetrahydrofolate,[37] supplementation with a folic acid preparation with increased capacity to cross the blood–brain barrier provides further stabilization of cofactor stores. N-acetylcysteine (NAC) is a potent antioxidant that increases extracellular glutamate[38–40] and has in one study[41] increased symptom resolution following blast-induced neurotrauma.

Analgesia

Although pain adversely impacts neurological recovery and stability in a variety of ways, no evidence-based treatment approaches exist.[42] Central and peripheral pain generators following TBI interfere with sleep quality; contribute to mood (depression and anxiety) dysfunction; provide an internal stimulus for distractibility and impaired concentration;[43] and most likely, directly impact memory, learning, and executive function through neurochemical interference with experience-dependent plasticity. Treatment with inappropriate analgesics or escalating doses of ineffective analgesics (especially narcotics) and centrally acting muscle relaxants to reduce spasm result in attenuated or disrupted cognitive recovery. Sleep disruption from mechanical, musculoskeletal, or positional factors reduces sleep efficiency, contributing to fatigue and neurocognitive compromise. Prefrontal mechanisms for redirecting attention and self-distraction are reduced following neurotrauma and impair mechanisms normally effective in suppression of noxious stimuli. Consequently, interventions targeted to reduce the number and intensity of pain generators is required to promote adaptive neuroplasticity. Comprehensive evaluation of inflammatory, discogenic, neuropathic, autonomic, and myofascial pain generators is central to development of target-specific interventions.

Positioning strategies while sleeping include the use of a sculpted foam pillow to maintain cervical alignment to reduce morning cephalgia, bolster use behind the knees to increase flexion to reduce stress on hips and knees, and pillows between the knees to decrease lumbosacral pain. Bruxism and temporomandibular (TMJ) generators can be reduced through a combination of preventive dietary management, nocturnal muscle relaxers, and topical anti-inflammatories (nonsteroidal or salicylate). Assessment for active trigger points, such as at occipital notches, insertion of splenius capitus and TMJ identify targets for injections/blocks for neuritic syndromes contributing to posttraumatic headache complexes.[44] Descriptions of lancinating cephalgia of rapid onset and resolution with or without concomitant lacrimation or rhinorrhea require further detailed assessment for partial seizure syndromes that frequently are misidentified as pain disorders.[45] The use of a structured, frequency-based, statistically validated interview will identify those individuals for whom a trial of anticonvulsants may improve this component of posttraumatic pain.

Hydration

In noninjured adults, studies define contradictory and variable results regarding the threshold for dehydration to impact cognition. Although some studies show reduced cognition after a 2%–3% loss of (water) body weight, multiple studies find that levels as low as 1% may adversely affect cognitive performance.[46] Neuropsychological performance on visuomotor, psychomotor, and cognitive tasks emerging with 2% body weight loss is normal.[47] Affective (anxiety/tension) and neurocognitive (visual vigilance and visual working memory) changes occur at that level.[48] Relatively mild states of dehydration occurring in the noninjured individual may have substantial adverse effects following neurotrauma.[49] Inadequate replacement from insensitive/passive loss in environments with high ambient temperatures or in higher altitudes decreases cerebral functioning even in otherwise stable neurological settings. Postinjury factors, such as reduced thirst, accelerated diuresis due to hypothalamic dysregulation, and general reduction in

self-observation capacity, combine to increase dehydration vulnerability. Shifts in electrolytes that would otherwise be adequately buffered against in a noninjured individual may, in an additive manner, reduce neurocognitive efficiency after neurotrauma.

Exercise

Devine and Zafonte define the beneficial effect of aerobic exercise in neuroplasticity, especially in the context of a systematic program of graded neurocognitive/neurobehavioral interventions after neurotrauma.[50] Although "learned helplessness" models have been cited for the success underlying various physical and neurophysiologic constraint-induced neurotherapy paradigms,[51] inactivity, passivity, and impaired initiation all reduce recovery potential after neurotrauma through a variety of synergistic mechanisms. Reduction in depression and improved function following brain injury has been noted after a systematic 10-week exercise protocol.[52] The observation of increased postconcussive symptom complaints associated with early exercise following concussive injury, especially in sports, has resulted in a systematic, graded hierarchy of return to exercise (and ultimately athletic engagement) as recently reviewed in the Ontario Neurotrauma Foundation's Second Revision of *MTBI Management Guidelines*. Although relatively infrequent, cardiovascular or neurovascular orthostasis syndromes must be considered in those with persistent symptomatology.[53] Although adverse effects of exercise in the acute phase postinjury are present, the positive influence of later exercise on experience-dependent plasticity via neurotrophin upregulation, improved cardiovascular tone or other means yet to be defined have been well established in animals and humans.[54]

PHARMACOLOGICAL ENHANCEMENT STRATEGIES

Once the domains outlined above are stabilized, attention may then be turned to the potential benefit of pharmacological agents to optimize neurochemical milieu. Stabilization alone may circumvent the need for any pharmacologic intervention in some situations. Comprehensive evaluation offers the optimum means to define treatment alternatives. Although no established evidence-based guidelines exist, a recent comprehensive review identifies current research and future needs.[3]

Several principles must be considered in this endeavor:

1. Neuronal communication involves a complex synergy among vitamin cofactors, monoamine neurotransmitters, neuropeptides, and neurohormones offering multiple potential intervention points.
2. Interventional efforts should best begin with those agents with the broadest influence and lowest toxicity potential and move to those with the most specificity and highest toxicity potential.
3. Optimizing the neurochemical milieu may require achieving levels that are, although within the normal distribution, at the high end of those ranges (2–3 SD above the mean) provided no individual coexisting medical contraindication exists.
4. Intervention strategies may employ the serial use or addition of agents (as occurs in antibiotic paradigms) or the immediate combined use of agents (as occurs in cancer chemotherapy) with which multiple targets are impacted simultaneously.
5. Adequate time to assess effect must recognize pharmacodynamics, pharmacokinetics, and route of administration aspects.

Cognitive stabilization

With age, the annual incidence of primary Alzheimer's disease increases from 53/1,000 in age 65–74 to 170/1,000 in age 75–84, to 231/1,000 over age 85.[55] Independent analysis by the Institute of Medicine has found a significant associative interaction between moderate TBI (RR 2.0) and severe TBI (RR 4.5) and dementia. Current intervention strategies for mild cognitive impairment (MCI) would appear to be prudent in the management of individuals with moderate-to-severe TBI to delay or attenuate functional decline.

Combined therapeutic approaches involving nutraceuticals (tetrahydrofolate, n-acetylcysteine, and vitamin B_{12}), central acetylcholinesterase inhibitors, and NMDA antagonists represent a multifocal intervention to stabilize and reduce the slope of deterioration over the aging process and prolong functional independence. Although no study currently exists to define the optimal time to introduce such an intervention, clinical experience indicates that absent the existence of a genotype either homozygous or heterozygous for APOE-$_4$, beginning treatment by age 55 is appropriate. Although given daily as a triple "cocktail," initial dosing is separated by a period of time adequate to assess for allergic sensitivity. In using cholinesterase inhibitors with combined acetyl and beta cholinesterase activity, neurobehavioral elements may be coincidentally tempered.

Anergia intervention

Dopamine has been demonstrated to be a critical neurochemical involved in engagement and learning.[56] Damage to frontal orbitofrontal dopaminergic pathways following neurotrauma has been linked to deficits in initiation of cognitive and volitional behavior.[57] Replacement strategies for dopamine have included trials of L-DOPA/carbidopa, dopamine agonists, monoamine oxidase B inhibitors, and dopaminergic potentiators.

Clinical experience and tolerability consistently identifies the utility of amantadine in promoting initiation in the setting of frontal neurotrauma where dopaminergic pathways are damaged.[58] Amantadine was originally developed as prophylaxis and treatment for influenza A. During that time, it was used in patients of all ages, from infants

to geriatric, and a serendipitous positive impact on those with Parkinson's disease was observed. Subsequent studies suggested dopaminergic (DA) interaction via several possible mechanisms, including reuptake blockade, facilitation of synthesis, and increasing postsynaptic DA receptor density.[59] Common side effects include reduced appetite (anorexia), dry mouth, insomnia, livedo reticularis, and nervousness. In older patients, urinary hesitancy and orthostatic hypotension may require dosage adjustment or discontinuation.

Therapeutic benefit of amantadine does not occur immediately. Dosage adjustments are made every 7–10 days in 100-mg increments until the desired clinical response is achieved, the maximum dosage is reached (300–400 mg in divided doses with meals), or a side effect develops. This period of dosage titration may require 3–4 weeks. To prevent difficulty with sleep initiation, the last dose for the day should be taken prior to 6 pm.

CAVEAT: DYSCOMPLIANCE VERSUS NONCOMPLIANCE AFTER FRONTAL LOBE INJURY

Lack of follow-through with therapeutic or medication interventions in medical populations has been largely described as *noncompliance*, a term that implies the willful refusal to adhere to an established treatment plan. Although deliberate insubordination may occur in provider-patient relationships, the roles of initiation and planning deficits following brain injury merit specific attention. Well-described dopaminergic pathways are responsible for initiation of volitional activity, motor or behavioral, in humans.[57] Over the first two decades of neurodevelopment, these circuits progressively branch, prune, and mature in a manner that parallels the diminishing degree of external structure, support, and supervision required by parents, teachers, coaches, and others as the child grows up. As a result, the degree of oversight required to ensure antibiotic medication compliance for an otitis media in a 5-year-old child is far more extensive than the same illness would require in a 15-year-old.

Frontal lobe involvement represents the region of the highest proportion of microhemorrhages following TBI,[60] and as such, a disproportionate likelihood of failure to comply with a medical treatment plan exists. Failure to comply in this injured population then represents a "dyscompliance" rather than a "noncompliance" state. Several potential contributors to such "dyscompliance" include impaired acquisition of new information, reduced speed of information processing, impaired efficiency in recalling or executing low-frequency events, and failure of natural supports to recognize the degree of functional impairment.

Just as no medication has been demonstrated as effective in reducing the need for parental oversight of the developing child, benevolent guidance and behavioral shaping is essential in minimizing the potential for dyscompliance. This includes event-specific oversight of medication administration that may then follow a pattern of decreasing external structure as the new behavior is "learned." Central to this concept is a professional recognition that desire to comply is not the deficiency.

CONCLUSION

Targeted pharmacotherapy following neurotrauma combined with the resolution of pain, stabilization of sleep, nutritional support, adequate hydration, and structured exercise creates an improved environment for experience-dependent neuroplasticity. Facilitative neuropharmacology represents a continuation of the hybridization of neuromedical, neurobehavioral, and neurorehabilitation interventions to maximize individual recovery and functional independence following neurotrauma. Future studies to best determine frequency, intensity, and duration of intervention will provide fine-tuning of this adjunct to neurorehabilitation and lifelong living.

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Assessment and management of mild traumatic brain injury

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INTRODUCTION

Mild traumatic brain injury (MTBI) or concussion was first identified as a syndrome in 1866 by John Eric Erichsen when he described a syndrome of multiple symptoms occurring following minor or severe head injury.[1] Controversy surrounding the diagnosis was soon to follow when an increase in the diagnosis of postconcussion syndrome (PCS) was noted by Reglar to coincide with the introduction of a compensation system in the United States.[2] Reglar concluded that the syndrome was due to a desire for financial gain, long inactivity, and fright. This debate has continued to the present day although neuroscience and medicine are combining to shed new light on the pathobiology of MTBI.

DEFINITION OF MTBI/CONCUSSION

There is no widespread consensus on distinctions that may exist between the terms *concussion* and *MTBI*. The terms are often used interchangeably.[3] The term *MTBI* was promoted by the American Congress of Rehabilitation Medicine in 1993 in an effort to reduce confusion around the term *concussion*.[4] It was thought that MTBI more accurately reflected the specific organ and injury. The definition adopted is as follows:

> A patient with mild traumatic brain injury is a person who has had a traumatically induced physiological disruption of brain function as manifested by at least one of the following:
>
> - Any period of loss of consciousness
> - Any loss of memory for events immediately before or after the accident
> - Any alteration in mental state at the time of the accident (e.g., feeling dazed, disoriented, or confused)
> - Focal neurological deficit(s) that may or may not be transient, but where the severity of the injury does not exceed the following:
>   - Loss of consciousness of approximately 30 minutes or less;
>   - After 30 minutes, an initial Glasgow Coma Scale (GCS) of 13–15;
>   - Posttraumatic amnesia (PTA) not greater than 24 hours[4].

A recent review of the literature[5] intended to develop an evidence-based guideline for concussion provided another definition of concussion that involved the following:

- A change in brain function after a force to the head that may be accompanied by temporary loss of consciousness.
- Indicators of concussion, identified in an alert individual after a force to the head that include the following:
  - Observed and documented disorientation or confusion immediately after the event;
  - Slower reaction time within 2 days postinjury;
  - Impaired verbal learning and memory within 2 days postinjury;
  - Impaired balance within 1 day postinjury.

Some shortcomings to this particular definition can be found in the requirement for comparative assessment of reaction time, verbal learning, and memory to a person's

baseline function within 2 days of injury and, similarly, balance within 1 day of injury. The clinician will require objective comparative baseline performance data to assess this objectively, which is unlikely to be available, or will need to rely upon the subjective comparison provided by the patient. Observation and documentation of disorientation or confusion can be difficult in the context of inconsistent availability of trained personnel at the event.

The American Association of Neurological Surgeons defines concussion as follows:

> A clinical syndrome characterized by immediate and transient alteration in brain function, including alteration of mental status and level of consciousness, resulting from mechanical force or trauma.[6]

The Fourth International Conference on Concussion in Sport in 2012[7] provided the following consensus statement:

> Concussion is a brain injury and is defined as a complex pathophysiological process affecting the brain, induced by biomechanical forces. Several common features that incorporate clinical, pathologic, and biomechanical injury constructs that may be utilized in defining the nature of a concussive head injury include
>
> 1. Concussion may be caused either by a direct blow to the head, face, neck, or elsewhere on the body with an "impulsive" force transmitted to the head.
> 2. Concussion typically results in the rapid onset of short-lived impairment of neurological function that resolves spontaneously. However, in some cases, symptoms and signs may evolve over a number of minutes to hours.
> 3. Concussion may result in neuropathological changes, but the acute clinical symptoms largely reflect a function disturbance rather than a structural injury and, as such, no abnormality is seen on standard neuroimaging studies.
> 4. Concussion results in a graded set of clinical symptoms that may or may not involve loss of consciousness. Resolution of the clinical and cognitive symptoms typically follows a sequential course. However, it is important to note that, in some cases, symptoms may be prolonged.

Although similarities between these definitions of concussion exist, debate remains in clinical practice as to whether the physiological disruption that occurs as a result of trauma results in transient, short-term, or long-term anatomical damage or neurophysiologic alteration. It should be noted that application of forces within each of the definitions above is not inherently those forces directly applied to the head. Rather, as in the case of blunt force trauma to the body, the forces may be transmitted through the brain from any direction.

Each definition highlights the idea that symptom presentation may or may not be transient. Carney et al. attempt to constrain the diagnosis to symptoms present within 1–2 days of injury.[5] Clearly, reliance in this definition on symptoms to be present within 1–2 days does not allow for delayed deafferentation or delays in seeking treatment and the opportunity for objective and independent documentation of symptoms. That said, assessment of MTBI or concussion is best performed immediately upon suspected injury. McCrea et al. found that immediate assessment was most accurate, and a delay of 24 hours limited the ability to obtain accurate assessment.[8] However, immediate and standardized assessment of consciousness remains relatively uncommon. Failing immediate and standardized assessment, the practicing clinician is left with history taking and correlation of reported observations immediately following injury and symptoms arising since injury to arrive at a diagnosis of concussion.

HETEROGENEITY OF INJURY

It is tempting to conceive of MTBI as a homogenous diagnostic entity; however, there is peril in doing so. Evidence exists for a gradation in the severity of MTBI.[8] In fact, many clinical guidelines have historically promoted a gradation of MTBI severity.[9,10] Variations in the biomechanics of any given injury, such as rotatory forces, direct or indirect forces, amount of force, and rates of deceleration will result in marked differences in the degree of injury.[11–14] Injury superimposed on various genotypes may result in different injury profiles, and factors such as body temperature and hydration at the time of injury, previous injury, gender, age, and intelligence appear to confound the progression of and recovery from MTBI. Stated alternatively, patient-specific factors contribute to the predisposition, or lack thereof, toward a particular outcome of a similar mechanical insult. An identical force, applied to separate individuals, can produce markedly different outcomes. Further, comorbid factors, such as the degree to which neuroendocrine disruption occurs, the presence of premorbid or postinjury substance abuse, concomitant sleep disorders, and others, can complicate prognostication. Consequently, it is important to examine each of the above factors and others as they may contribute to the nature and extent of injury to the brain as each may assist the clinician in understanding the resolution, persistence, or progression of symptoms in different patients. Table 19.1 contains factors likely to contribute to the heterogeneity of MTBI.

PREVALENCE

The prevalence of MTBI has been estimated in various forms ranging from 100 to 600 per 100,000.[15] Wide variability in

Table 19.1 Contributing factors to disease heterogeneity in MTBI

- Biomechanics of injury
  - Amount of force
  - Rotational force
  - Rate of deceleration
- Severity of injury
  - Loss of consciousness
  - Posttraumatic amnesia
  - Skull fracture
- Genomic
  - APOE-4 allele
  - Hereditary predisposition to other neurodegenerative diseases
- Previous cumulative injury
- Intelligence
- Education
- Vocation
- Age
  - Brain maturation
  - Brain aging
  - Age-related endocrinologic status
- Gender
- Physiological conditions at injury
  - Temperature
  - Hydration
  - Stress
- Co-morbid conditions
  - Sleep disorder
  - Substance abuse
  - Psychiatric conditions
  - Endocrine dysfunction

these figures arises from varying methodologies, operational definitions, populations, insurance availability,[16] and geographical factors of the incidence literature. Thurman and Geurrero reported a drop in hospitalization associated with MTBI from 130/100,000 in 1980 to 51/100,000 in 1995.[17] The majority of studies undertaken involve review of emergency department attendance or hospital discharges. However, it has been estimated that such approaches severely underestimate the actual incidence of MTBI, leaving many MTBIs unrecognized.[18,19] The CDC has estimated that MTBI arising from sports-related activities alone in the United States accounts for between 1.6 and 3.2 million cases per year.[19] The literature provides identification of a higher incidence in males versus females (RR for males ranged from 1.9 to 2.5). Incidence appears higher in African Americans than Caucasians (RR = 1.35)[20] except African Americans living in inner city areas versus Caucasians living in suburbs in North American studies (RR = 2.8).[21] The incidence in studies of active military populations varies by age, race, and gender.[22]

In large measure, the prevalence of MTBI appears to be higher in males than females when considering injuries that are not sports-related. However, rates of injury for sports-related MTBI are higher for females in studies that make comparisons between same-sport participation in high school- and collegiate-aged populations.[23–26] Higher same-sport incidence in females may be related to anatomic differences in skull thickness and dimensions in comparison to males, affording females less protection from externally applied forces.

Differences in outcome associated specifically with gender are less well investigated. A recent systematic analysis reported that females may show a higher risk of epilepsy—more so for children and young adults.[27] Females are also more likely to commit suicide and tend to use more health care services. Males show a higher tendency toward development of schizophrenia.

The vast majority of individuals who sustain MTBI or concussion experience resolution of symptoms within about 90 days of injury.[28] A minority of individuals, however, will experience prolongation of symptoms or progressive development of symptoms extending beyond 90 days.[29] It is unclear why these individuals experience the development and/or progression of symptoms.

Several factors such as severity of injury, genomic factors, neurophysiologic conditions at the time of injury, previous neurologic injury, substance abuse, delayed deafferentation, or other co-occurring conditions, such as pituitary dysfunction or sleep disorders, may contribute to symptom persistence. In some, delayed deafferentation may occur following the initial injury.[30] Brain atrophy studied on a longitudinal basis was found to be progressive in a small group of MTBI patients, suggesting both a progression in a disease process as well as an association of degree of atrophy to severity of injury.[31] More severe injuries, as distinguished by loss of consciousness, showed greater changes in brain parenchymal volume across time. These changes warrant longer follow-up for patients who may actually progressively develop symptoms.

SYMPTOMS AND DYSFUNCTION FOLLOWING MTBI/CONCUSSION

Common symptoms of MTBI can include the following:[6]

- Prolonged headache
- Vision disturbances
- Dizziness
- Nausea or vomiting
- Impaired balance
- Confusion
- Memory loss
- Ringing in the ears
- Difficulty concentrating
- Sensitivity to light
- Loss of smell or taste

Dysautonomia has also been identified as a potential complication following MTBI.[32,33] The mechanism of the dysautonomia has been hypothesized to possibly include compromise of brain stem structures as evidenced by brain stem evoked potential and EEG study.[34] Others conceptualize dysautonomic response more specifically as dysfunction of neuroanatomic cardiovascular regulation.[33] Neuroanatomic cerebrovascular dysregulation involves irregularities in cerebral blood flow, cerebral perfusion pressure, cerebrovascular resistance, and/or cerebrovascular reactivity.[33,35] Cerebrovascular reactivity and carbon dioxide, as a potent cerebral vasomotor agent, may be at the center of neuroanatomic cardiovascular regulation.[33]

The condition has been most fully explored in the context of sports-related concussion.[36–38] Transient suppression of the available range of heart rate variability has been found in concussed athletes wherein less heart rate variability has been associated with prolonged difficulty after concussion.[38] Dysautonomia has also been implicated as important in the differential diagnosis of chronic dizziness following MTBI.[39] Dysautonomia may contribute to exertion-based exacerbation or provocation of symptoms.

MTBI can induce posttraumatic epilepsy (PTE).[40,41] Seizure activity after MTBI tends toward complex-partial seizures rather than tonic-clonic seizures. In a group of 3100 individuals with a diagnosis of PCS, generalized or focal EEG abnormalities were found in 60% (59% generalized; 41% focal) of subjects.[41] Of the focal abnormalities, 28% were localized to temporal lobe structures. It should be noted that some of these individuals sustained a loss of consciousness that would exceed today's common time frames for a diagnosis of MTBI. Clinical manifestation of temporal lobe epilepsy (TLE) can include stop-stare phenomena, lip smacking, hallucinations, paranoia, mania, hyper-religiosity, and stereotypic behaviors.[42] TLE comprises about 20% of posttraumatic focal epilepsy.[43] TLE can manifest also in variations in sexual behavior, including hyposexualism, hypersexual episodes, fetishism, transvestism, loss of libido, and exhibitionism.[44,45] Consequently, psychiatric diagnoses or changes in sexual behaviors may be actually related to PTE and potentially associated with MTBI.

MTBI can result in damage to the hypothalamic-pituitary axis and a consequent number of neuroendocrine disorders. Such disorders have been identified in 37% of individuals with MTBI.[46] Axis impairments include the somatotroph, gonadal, thyrotroph and adrenal axes, in order of prevalence. These disorders can result in both subtle and overt clinical symptoms, the most impactful of which may be fatigue, exercise intolerance, weakness, anxiety, daytime somnolence, weight gain, hyperlipidemia, osteoporosis, impaired processing speed, sleep disorders, and depression. The reader is encouraged to review the chapters pertaining to endocrine function in this text.

It is unclear as to when metabolic stability is achieved after an injury. Animal studies suggest a return to baseline in glucose metabolism at about 10 days post fluid percussion injury.[47] However, metabolic disruption has been observed to persist for as long as 30 days in athletes sustaining a single concussion and up to 45 days for those who sustain a second concussion prior to 30 days following an initial concussion.[48] Many of the return-to-play guidelines fail to directly consider these findings, favoring instead approaches that center on graduated return to activity dependent upon repeated assessment using symptom provocation and reporting.[7,49] Clearly, the literature is not sufficiently developed to warrant more significant precautionary time frames.

There seems to be growing consensus about the cumulative nature of MTBI. Carlsson et al. reviewed symptoms of PCS, self-assessed health variables, finger tapping, and reaction time in 1,112 men from three age groups (30, 50, and 60 years of age) in Sweden.[50] The findings pointed to the cumulative nature of repetitive injuries on these variables while age did not appear to affect sequelae. Today, conditions such as chronic traumatic encephalopathy may represent evidence of long-term neurophysiological consequences of repetitive MTBI.[51–53] There is also a growing body of evidence that endocrine and immune system alteration associated with MTBI may underlie the development of other chronic neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, and amyotrophic lateral sclerosis.[46,54–63] A variety of tauopathies, mitochondropathies, gliopathies, and myelinopathies may be eventually causally linked to neurophysiologic alteration associated with MTBI. As knowledge of the pathophysiology of the brain after MTBI improves, disease prevention and mitigation may become a greater focus.[64,65]

POSTCONCUSSION SYNDROME

Patients with persistent symptoms are said to experience PCS.[66,67] Comprehensive, accurate diagnosis and effective management are of paramount importance for these patients. Symptom persistence beyond 1 year can be expected in between 5% and 20% of cases.[68] Patients who develop PCS represent the primary population for more significant medical and rehabilitative intervention at present.

Prognostication as to which patients may experience symptom persistence is both important and difficult. Although recovery from a single, uncomplicated MTBI can be expected to result in no long-term symptoms in the majority of patients,[69] it can be difficult to know whether an MTBI for any given person is their first and only.

The factors listed below appear to contribute to symptom persistence:

1. Severity of injury (LOC)[70]
2. Genome upon which injury is imposed (e.g., APOE4 allele positive)[71]
3. Comorbid substance abuse[72]
4. Postinjury education/expectations[73,74]
5. Gender[72,75]
6. Age as associated with suicide[72]
7. Cumulative injury[50]
8. Elevated serum protein S-100B[76]
9. Dizziness[76]
10. Headache[76]
11. Skull fracture[76]

Patients who go on to develop PCS may experience additional complications beyond the common symptoms following concussion listed above. These can include verbal learning deficits, speed of information processing deficits, iatrogenic complications, persistent oculomotor and upper extremity visuomotor impairment, psychological and emotional secondaries, seizures, family system issues, employment compromise, and financial issues.[70,77–79]

Patients who experience PCS may report a loss of confidence in medical treatment, and others may more aggressively pursue medical consultation in an effort to find relief for their symptoms. Either experience can logically contribute to anxiety arising from the duration of symptoms and sometimes the perceived or actual worsening or progression of symptoms. Patients who do not find relief in medical consultations sometimes report feelings that medical treaters or members of their social circle do not believe their symptoms. Others may be unaware of their symptoms or unwilling to accept them as real when reported by reliable sources, such as family, close friends, or professionals. Consequently, accurate documentation of an injury and all relevant factors can be crucial. Some patients with PCS may develop psychotic disorders, schizophrenia in men, depression, difficulty sleeping, anxiety, paranoia, panic attacks, suicidal ideation, or suicide.[72,75,78,80] The risk of suicide after MTBI without comorbid substance abuse was three times greater than the general population and may be greater in women than in men.[27,72] The risk of suicide increased to five times that of the general population in those with MTBI and comorbid substance abuse.

DIAGNOSIS AND DOCUMENTATION

Recommendations for use of a standardized management of concussion come from several credible sources, one of the most frequently cited being the Sport Concussion Assessment Tool 3 (SCAT3).[7,81] Additionally, the Acute Concussion Evaluation provides for physician management and return-to-school planning for both the physician, school personnel, the patient, and the family.[82]

In considering a diagnosis of concussion or MTBI, it is useful to undertake and document the following with the assistance of a family member or close associate when practical:

Medical

1. Determine whether consciousness was lost.
2. Determine the duration (or estimate) of loss of consciousness.
3. Determine whether there was an alteration of consciousness (dazed, stunned, disoriented, or confused).
4. Determine duration of alteration of consciousness.
5. Determine the presence of retrograde or anterograde amnesia.
6. Determine the duration of PTA.
7. Document key information pertaining to the biomechanics of the injury.[83,84]
   a. Amount and nature of force
   b. Rotatory forces present
   c. Accompanied by fall
   d. Size and speed of vehicles or objects struck by or against
   e. Damage to vehicles or objects struck by or against
   f. Detail all other bodily injuries sustained
8. Conduct neurological examination.
9. Determine medication history.
10. Determine alcohol use patterns.
11. Determine preinjury and current substance abuse history.
12. Determine preinjury and current caffeine intake characteristics.
13. Determine preinjury and current nicotine intake characteristics.
14. Evaluate for fatigue.
15. Evaluate for sleep disorders.
16. Evaluate for signs of dysautonomia.

Vestibulo-ocular function

1. Evaluate balance and vestibular function.
2. Evaluate oculomotor function.
3. Evaluate for light, sound, and motion sensitivity.

Cognitive function

1. Evaluate visual-perceptual function.
2. Evaluate speed of information processing.
3. Evaluate attentional skills.
4. Evaluate concentration skills.
5. Evaluate short-term, long-term, and working memory.

Psychological function

1. Evaluate for depression.
2. Evaluate for anxiety.
3. Evaluate for awareness/denial.
4. Evaluate for mood swings and irritability.
5. Determine preinjury psychological status and history.

Academic/vocational history

1. Determine academic achievement and performance.
2. Determine history of learning disabilities or attention disorders.
3. Determine vocational history, positions, and position durations.

Social

1. Determine leisure pursuits to include hobbies, athletics, and other recreational pursuits.
2. Determine social history.
3. Determine legal history.

The clinician must be cognizant of the motivational differences in reporting observed between athletes and nonathletes as competitive athletes or even some others may be prone to under-reporting symptoms.[85] This may necessitate more persistence in the patient interview to effectively investigate and document potential injury.

It is standard practice to characterize the patient's past medical history and family medical history. A detailed

review of the comprehensive neurological examination is not reviewed herein. The neurologic exam for the patient with MTBI is more expansive with careful attention necessary to vestibular, oculomotor, and executive cognitive function.

Careful examination of cranial nerve function in the patient with PCS will likely reveal abnormalities in oculomotor control and oculovestibular function. Examination by a neuro-ophthalmologist or neuro-optometrist allows for objective measurement of oculomotor and visual perceptual function. Screening of oculomotor function can be conducted by an experienced occupational therapist along with detailed objective testing of visual perceptual functions. Careful evaluation of vestibulo-ocular reflex is important and can be facilitated by referral to otolaryngology or audiology in some instances. Some evidence is found for enhanced detection of balance disorders by increasing cognitive load during gait.[86,87]

A review of medications should be undertaken, paying attention to prescription, nonprescription, and dietary factors and herbal remedies for potential side effects and interactions. This inquiry can prime recall for the patient with attention or memory disturbance to recall other complaints or concerns. Self–reporting should be corroborated by a close friend or family member due to the potential for high-level cognitive dysfunction. A patient's medication history may require chronicling and/or corroboration, in particular, if the patient is several weeks or longer from the date of injury. Iatrogenesis is a common finding in the chronic management, or mismanagement, of MTBI. To that end, pain complaints will often have been treated with numerous analgesics and modalities in the patient with chronic PCS. MTBI may be accompanied by other bodily injury, such as musculoskeletal injury. Protracted use of analgesics can lead to polypharmacy and development of iatrogenic rebound headache phenomena that can become severe and debilitating. Medication and dietary (caffeine consumption, in particular) histories for patients with chronic daily headache should be carefully reviewed with an eye toward subsequent intervention.

Iatrogenesis is a common finding in clinical practice with PCS. Iatrogenesis can arise from medication with prescription medications or recommended use of over-the-counter medications as well as with self-directed use of caffeine, alcohol, over-the-counter medications, or illicit substances. These can include sleep agents, antidepressants, anxiolytics, analgesics, neurostimulants, and anticonvulsants. Imperfect medical care can occur by virtue of a lack of experience by the practitioner, incomplete or inaccurate information coming to the practitioner from the patient or family, or uncoordinated treatment with other medical disciplines. Symptoms and potential medication side effects should always be considered for possible causal linkages. Some evidence points to changes in the blood–brain barrier (BBB) that may explain changes in how substances enter and leave the brain.[88,89] In general, less may be more in terms of pharmacological intervention. However, properly targeted pharmacological treatment is the real key.

Loss of consciousness has been associated with increased severity of injury and greater symptom presentation.[8] It is also associated with a longer delay in recovery to baseline neurocognitive function. That said, a loss of consciousness is not necessary to induce concussion or to result in persistent symptoms that fail to resolve spontaneously.[4] Hence, it becomes important to document not only a loss of consciousness and reported duration, but also signs of alteration of consciousness, such as feeling or appearing dazed, stunned, disoriented, or confused and duration of such.

Imaging results following MTBI may include skull X-rays, CT scans, or MRIs. There has been correlation noted between the presence of skull fracture and the development of PCS.[76] A fracture of the skull connotes a level of force applied to the head and potentially transmitted across cortical and subcortical structures and should be considered in the conceptualization of the biomechanics of the injury itself.[90] Open field MRIs may provide less information than closed units, and magnet strength is a significant factor in the identification of lesions in the brain.[91] In fact, the addition of early MRI to CT scanning results enables better outcome prediction.[92] As many as 27% of patients with normal CT scan findings showed abnormal findings on early MRI.

Investigation and documentation of retrograde or anterograde amnesia immediately surrounding the trauma can provide additional information as to the severity of injury. In moderate-to-severe brain injury, duration of PTA has been found to correlate with injury severity.[93–95]

Alcohol and substance abuse have been associated with TBI both in terms of comorbidly occurring conditions and as factors impacting outcome after TBI.[96,97] Alcohol use after TBI has been associated with a preinjury abuse of alcohol, male gender, younger age, a diagnosis of depression since TBI, mental health status, and physical functioning.[98] Patients with alcohol or substance abuse concerns may evolve to greater reliance upon these substances as part of a self-medication regimen.

Use of caffeine and nicotine as stimulants can be observed to increase in some individuals postinjury as these people attempt to improve attention, concentration, overall arousal, and cognitive function. Caffeine can be useful as a neurostimulant, however, given a range of multiple dose half-lives of between 7 and 8.5 hours, caffeine can seriously disrupt sleep in some patients who overuse it and may facilitate the development of a stimulant irritability.[99] Disruption of sleep cycles is common following MTBI.[100] Sleep is crucial for immune and endocrine function as well as to ward off daytime somnolence, fatigue, and irritability. Furthermore, caffeine withdrawal headache and chronic daily headache can be problematic in patients using caffeine as caffeine.

Headache pain is a frequent complaint following MTBI, occurring in up to 85% of patients who develop PCS.[101] Reports of headache diminish as time progresses from injury from a high of more than 50%, decreasing to 26% at 3 months, 16% at 6 months, and 9% at 1 year. Headache can

have numerous etiologies, and each of these must be considered in the clinical presentation of headache. Etiologies may be unrelated to MTBI and can include migraine etiologies, cluster etiologies, tension headache associated with musculoskeletal strain/sprain injuries in the cervical or shoulder region or vestibular sensitivity, sinus infection, temporomandibular joint dysfunction, or substance abuse/withdrawal. Consequently, careful characterization of the headache pain itself and consideration of potential contributory etiologic factors must be undertaken.

Developing a comprehensive and substantiated view of the patient's preinjury academic and vocational achievement is important as is rounding out intellectual and personality characteristics of the patient. Many people can provide a rough approximation of their academic achievement and topic strengths; however, it can be quite useful to request actual academic records. These are more immediately available for younger patients; however, school report cards may provide insight into relative strengths in various topic areas together with any standardized testing that might be available and behavioral insights. Records may also provide information concerning the presence of preinjury learning disabilities.

Similarly, a chronologically accurate depiction of a patient's vocational history can provide important information about basic worker characteristics, personality, vocational outlook, and achievement. The personal history should include an understanding of leisure pursuits, including hobbies, athletics, and recreational activities. Understanding these will also inform the examiner about necessary advisory precautions for activities that may expose the patient to reinjury prior to recovery. Lifestyle counseling may be in order so as to undertake an informed decision-making process about activities the patient may be better off avoiding.

Finally, the examiner should inquire about social and legal histories. Information about family of origin, family structure, living arrangements, marital status and history, and legal matters, such as arrests, convictions, lawsuits, and other legal actions can be important factors in the overall approach to diagnosis and treatment after concussion. It is important to position these findings with objective clinical findings in order to best determine the degree to which any particular factor may be impacting a patient's clinical course.

In undertaking the comprehensive process described, the complete picture surrounding the trauma to the brain can be best understood. Given that a percentage of individuals who sustain a concussion will go on to develop persistent symptoms and that endocrine dysfunction may emerge 3 to 6 months postinjury and can affect approximately 37.5% of individuals after MTBI, it stands to reason that these patients should be followed over a longer period of time.[102] One-time evaluations become unacceptable in this light.

TREATMENT

The patient and family should be advised that gradual symptom resolution is most probable and provided information about adequately balanced rest and graduated return to activity. However, they should also be advised to be alert to the possibility of symptom persistence or worsening or new symptom development. All of these are reasons for medical attention.

The patient and family must be educated about avoiding activities that may increase the likelihood of another concussive blow to the head during recovery and perhaps for the longer term, depending upon the patient's history and severity of clinical symptoms. Treatment should begin with education about concussion and likely symptoms. Although some concern exists for providing would-be malingerers with information about symptom endorsement, the literature provides support for better outcomes associated with proper patient education.[103–105]

The vast majority of patients sustaining concussion go on to experience symptom resolution within 90 days of injury.[68] Individuals reporting two or more symptoms decreased across a 12-month period from 65% to 13% when patients lost to follow-up were considered asymptomatic.[29] However, those individuals for whom follow-up was maintained showed a decrease in those reporting symptom persistence of two or more symptoms across a 12-month period from 67% to 40%. In the latter group, complaints of memory and dizziness increased at 3 months from 14% to 18% and 16% to 23%, respectively. Headache decreased for all individuals at both 3 months and again at 12 months. The symptom persistence reported by these authors necessarily informs likely findings in patients with PCS.

There has been insufficient study of the relationship between activity and rest levels immediately postconcussion to precisely determine the degree to which these factors may impact symptom persistence. Animal studies point to a period of time during which activity immediately postinjury contributes to additional neurologic injury as well as a period of time that may represent a better time frame for neurophysiologic rest prior to restitution of normal neurophysiologic demand.[106] Athletes who sustained concussion were found to experience the best recovery of verbal memory, visual memory, visual motor speed, and reaction time with moderate levels of activity in return-to-school activity and light physical activity as compared to both lesser and greater levels of engagement.[107] Building on this evidence, the most recent guidelines for return to play for athletes who sustain concussion incorporate a period of rest with a graduated return to play that promotes provocation testing by progressively greater activity levels over a roughly 2-week period of time.[49] Although these guidelines are specific to athletic participation, similarly cautious approaches to returning to school or work are increasingly utilized and are discussed later in this chapter.

Treatment should include a rather longer period of follow-up to ensure that symptoms have not increased at 3 months and have, in fact, dissipated. Similarly, pituitary dysfunction is not likely to evoke frank symptoms in less than 3 months as distinguishable from those symptoms

of the concussion itself. Symptom persistence may herald endocrine testing.

The findings from a comprehensive diagnostic approach should encompass medical, vestibular, oculomotor, visual-perceptual, cognitive, psychological, and vocational domains and will determine the treatment program design. Individuals who go on to develop PCS will require additional and more comprehensive diagnostics and treatment as soon as practical. The diagnostic arenas to be considered have been covered previously.

Medical oversight should be integrated with therapies to assure a careful assessment for application of judicious pharmacological supports, iatrogenic complication, psychological complications, and behavioral matters potentially associated with diet and sleep. Iatrogenic complications are quite common in individuals with PCS, especially so for those with prolonged symptoms of a year or longer. Headache pain must be differentially diagnosed to distinguish migraine, cervicogenic, neuritic and neuralgic, tension, sinus, cluster, posttraumatic migraine, and chronic daily headache.[108] The latter is more common in prolonged PCS, can be related to medication overuse (medication overuse headache, MOH) and can be difficult to treat given the need to wean the patient from offending substances or medications.[108,109] Musculoskeletal injuries that accompany some concussions may be treated on a prolonged basis with analgesics. Reviews of chronic PCS patient histories will often reveal a complicated course of single and polypharmacy with the emergence of chronic daily headache or progression from sporadic headache to chronic daily headache.

These patients require education and supportive reassurance as to the iatrogenic nature of the headache pain, use of adjuvant therapies for relief of pain, and possible integration of physical and psychological therapy modalities to address either the underlying pathologies of localized pain (e.g., ultrasound for deep muscle pain) or to facilitate pain management during detoxification. Effective therapies may include relaxation, hypnosis, or meditation in addition to general counseling. The physician must be cognizant of the tendency toward self-medication and under-reporting in patients with PCS. Self-medication occurs often in the form of caffeinated beverage use, nicotine, and over-the-counter analgesics containing caffeine. Generally speaking, less is more when dealing with pharmacologic management of PCS.

Iatrogenic complications are also associated with inexpert application of psychiatric medications. The PCS patient displaying psychotic symptoms may be better served by careful review for sleep deprivation and/or TLE. Clearly, episodes of psychosis require acute interventions. Long-term interventions, however, should rule out TLE and sleep disorders.[41,110] Documentation of TLE can be difficult in that usual montages utilized for EEG can disallow detection of temporal lobe foci. EEG undertaken in specialized settings can be more accurate. That said, empirical approaches might be required that rely upon documentation of suspected symptoms attributable to TLE that are reduced with application of anticonvulsant coverage be required.

Similarly, the use of antivertiginous drugs for management of dizziness should be avoided except in the most severe of cases. These medications work by reducing the responsivity of the vestibular end organ. Although the exact cause of vestibular hypersensitivity following concussion can vary from end-organ pathologies to involvement of the vestibulocerebellar, vestibulo-ocular, or vestibulospinal pathways to involvement of cortical vestibular sensory regions, treatment usually relies upon progressive movement therapies designed to desensitize or habituate vestibular response. In rare instances, the system is hyposensitive to movement. Therapies for both hypersensitivity and hyposensitivity are largely similar. Medications that reduce end-organ response will frustrate this effort. The use of antiemetic medications is also discouraged, except in the most severe cases, due to the antagonistic dopaminergic effect of the drugs.

Patients with dysautonomia may present with neuroanatomic cardiovascular regulatory problems and will, undoubtedly, undergo extensive cardiologic workup. Once cleared for cardiologic abnormalities, these patients must undergo a progressive return to their normal cardiovascular exertional capabilities under medically supervised physical therapy. It is unclear as to whether prescribed rest is beneficial to or accelerates recovery from neuroanatomic cardiovascular regulatory disorders.[111] Given that patients cannot tolerate cardiovascular stress well and manifest with exacerbation of vestibular and headache symptomology, it may be that nature, itself, imposes a period of rest via these responses. Physical therapy will be necessary to address deconditioning.

Disturbances of sleep are common in PCS.[112] Common disorders observed include hypersomnia, circadian rhythm disorders, periodic limb movement disorder, insomnia, poor sleep hygiene, narcolepsy, and sleep apnea/hyponea.[113–116] Sleep disturbances can negatively impact cognitive function and can lead to further neurologic damage.[117–122] Sleep is important for neuroendocrine and immune system function as well as memory.[123–126] Detailed sleep evaluation by qualified sleep medicine physicians must be undertaken for patients with PCS who demonstrate a high probability of sleep disorders with appropriate interventions.

Patients with prolonged oculomotor deficits may develop persistent visual-perceptual dysfunction. Visual-perceptual disorders can be subtle, and some patients will endorse difficulties, such as reading discomfort or delayed processing speed; reduced reading comprehension; blurred vision; and difficulties in driving, working, or leisure pursuits. Oculomotor and visual perceptual deficits can exert profound impacts on academic, vocational, and social participation and performance.

Treatment for oculomotor and visual perceptual disorders can be completed by occupational therapy or in some neuro-optometry practices. Oculomotor and visual perceptual therapies can be quite effective and are provided in other chapters of this text. Neuroparalytic strabismus repair surgery may be necessary in the instance of orbital fractures

or severe dysconjugate gaze. Generally, however, these procedures should be reserved for failure of neuromotor therapies to correct oculomotor function and ocular alignment or until a period of recovery has been allowed, usually 12 months.

Anomia and ageusia may be identified. One study reported 44% of individuals with MTBI demonstrated impaired olfaction.[127] Relatively fewer interventions exist for these problems. Some evidence for improvement of olfactory function via zinc supplementation can be found.[128] Given the neuroanatomic proximity of the olfactory system to the circuitry of the orbital frontal cortex, olfactory disturbance may not be recognized by the patient and may herald difficulties with affect recognition in others and the ability to experience empathy, thereby impacting social interaction.[129]

Depression in PCS may be treated with a combination of psychotherapy, medication, hormone replacement, and exercise. Selection of medication should consider the desired neuromodulatory effect, taking care to discern whether the drug will impact a single or multiple neurotransmitter systems. Patients presenting with obsessive-compulsive disorders, sleep disturbances, irritability, anxiety, and depression may benefit by application of SSRI or SNRI medications.[130–132] Depression may predate a concussion, or may evolve postinjury.[133] The etiology of depression must always be carefully determined. In a study of concussed male athletes, fMRI demonstrated reduced activation in the dorsolateral prefrontal cortex and attenuated deactivation in the medial frontal and temporal regions wherein neural responses were found to be correlated with the severity of depression.[134] Gray matter loss in these same areas was demonstrated. A smaller study of concussed female athletes failed to show similar findings; however, elevations of glutamate/glutamine, a marker of excitatory neurotransmission, were found in the chronic stages postinjury, commensurate with elevations noted in the general population and in professional athletes.

Persistent cognitive disorders will impact the individual's ability to perform academically, vocationally, and socially. It is important to attempt to document cognitive status early and monitor for changes in status across the first 3 months postinjury. Those patients whose symptoms persist will require detailed examination of cognitive function, perhaps via formal neuropsychological evaluation, and intervention via cognitive rehabilitation. Combination therapies involving cognitive rehabilitation, pharmacotherapy, and endocrine replacement may be required, dependent upon the nature of the clinical deficits identified.

Primary cognitive deficits in PCS include deficits in attention, concentration, processing speed, and memory. Sleep disorders, PTSD, depression, pharmacologic iatrogenesis, and endocrine disorders may all contribute to cognitive deficits and so must be addressed in a comprehensive fashion. More commonly, treatment for the cognitive disorders can be objectively documented by speech pathology or neuropsychology. Speech pathologists and some neuropsychologists and occupational therapists may also provide cognitive therapy.[135,136]

To the extent that cognitive deficits are present, return-to-learn and return-to-work protocols should be adhered to carefully. Prematurely returning to learning or work may seriously imperil the individual's academic or vocational career. The physician and treatment team must advise patience and caution in returning to learning or work. Return-to-learn protocols provide for modifications of expectations for performance similar to return-to-play athletic protocols.

Students and workers may require active supports and accommodations early in their recovery that can be gradually diminished over time as recovery occurs. Individuals should not undertake critical testing or dangerous or crucial job functions during this time frame lest cognitive or other symptoms impact or impair their performance. They may require accommodation, such as longer time periods to complete assignments or tasks. They may demonstrate less tolerance for stressful situations or difficult, complex tasks. In fact, cognitive demands that exceed their recovery status may evoke additional symptoms such as headache, dizziness, fatigue, or irritability. Any of these could have significant ramifications for grading or job performance if coworkers, supervisors, fellow students, or teachers are unaware of the need for reduced demand and accommodation, including serious academic failure or termination of employment. In a study with a small sample size, a period of 1 week of complete rest was found to preferentially change cognitive testing and total symptom scores.[111] However, as described earlier, other evidence suggests that moderate activity appeared preferential to complete rest or unmoderated activity. Clearly, the population is not a homogenous one, and consequently, it will likely remain somewhat difficult to assert a single pathway for patients with concussion. Understanding that rest plays a role is important along with graduated and monitored return to preinjury levels of function. It is, thus, important to provide for continued monitoring of patients through complete recovery lest deterioration, which occurs in some patients, manifests and goes unrecognized.

HISTORY IN THE MAKING

Legislation to guide concussion prevention, diagnosis, and treatment in sports, in particular, has done a great deal to increase public awareness of MTBI. Every state in the United States now has legislation pertaining to concussions in sports in one fashion or another. The first of these efforts began in the northwest region in 2009 with the Lystedt Law in Washington. The law held three key provisions pertaining to education for student athletes and parents, removal from play, and return-to-play restrictions and medical clearance. The National Football League (NFL) became instrumental in encouraging passage of similar legislation around the country in concert with efforts by brain injury advocacy groups, such as the Brain Injury Association of

America. Components of the laws vary from state to state but include education and/or training for coaches, trainers, and parents; removal from play for suspected concussion; medical clearance before return to play; annual training requirements for coaching staff; return-to-school learning activities and criteria; and limits on contact in practices. Rules changes in various sporting contests have been implemented in an effort to reduce the overall incidence of concussion. There are, however, few provisions for enforcement efforts within these laws at this time.

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20

Chronic traumatic encephalopathy

ANN C. MCKEE

INTRODUCTION

The concept that repetitive blows to the head can induce long-lasting cognitive and behavioral difficulties was first recognized by boxing enthusiasts and fight promoters nearly a century ago although the first report in the medical literature was made by Harrison Martland in 1928. Martland was a pathologist, yet he described a clinical syndrome of progressive neurological deterioration in boxers, a condition known as "punch-drunk."[1] Over the decades that followed, the condition was referred to as "dementia pugilistica,"[2] "the psychopathic deterioration of pugilists,"[3] "traumatic progressive encephalopathy,"[4] and eventually, "chronic traumatic encephalopathy."[5] By the 1990s, the term chronic traumatic encephalopathy (CTE) was in wide use, highlighting the concept that the neurodegeneration after trauma was not restricted to boxers[6,7] and could be found in men and women exposed to a wide variety of repetitive mild closed head injury, including physical abuse,[8] head-banging,[7,9] rugby,[7] poorly controlled epilepsy, and "dwarf-throwing."[10] More recently, CTE was reported in American football,[11–14] soccer,[15] ice hockey, and baseball.[14,15] In addition, some military veterans exposed to repetitive concussive and explosive blast injury were found to have CTE.[14,16–18]

NEUROPATHOLOGY

History of the neuropathological characterization

The first neuropathological descriptions of CTE were case reports or small case series of boxers who were described to have cerebral atrophy, enlarged ventricles, and cavum septum pellucidum with silver-positive neurofibrillary tangles (NFTs) in the cortex and brain stem on microscopic examination.[3,19–23] In 1973, the first large case series was reported by Corsellis, Bruton, and Freeman-Browne, who described the clinicopathological features of 15 male former boxers, ranging in age from 57 to 91 years. Pathologically, Corsellis and colleagues described reduced brain weight, enlargement of the lateral and third ventricles, thinning of the corpus callosum, cavum septum pellucidum with fenestrations, scarring and neuronal loss of the cerebellar tonsils, and neurofibrillary degeneration of the cerebral cortex and substantia nigra on Von Braunmühl's silver stain.[24] Beta amyloid (Aß) plaques were found in 20%. The first case of CTE in a female, a 76-year-old woman who had experienced decades of physical abuse and developed prominent memory loss, confusion, and dementia several years before her death, was reported by Roberts and colleagues.[8]

Early lesions of CTE were subsequently described in a second woman, a 24-year-old with autism and prominent head-banging behaviors.[9] Neuropathological examination showed perivascular clusters of thioflavin and Gallyas positive NFTs and neurites at the depths of the cerebral sulci and in the superficial layers of the inferior temporal, entorhinal, and perirhinal cortices, in the absence of Aß plaques.[9] Hof and colleagues also observed that NFTs were distributed in the superficial cortical layers in CTE, a laminar distribution similar to two other environmentally acquired tauopathies, postencephalitic Parkinsonism and Guamanian Parkinsonism dementia complex (GPDC), that is not found in Alzheimer's disease (AD).[25] Using immunohistochemical techniques for tau, Geddes and colleagues described patchy, perivascular deposits of hyperphosphorylated tau (p-tau) in the brain of a 23-year-old boxer. Geddes compared the immunohistochemical findings of the young boxer and four other young men, ranging in age from 23 to 28 years (mean 26 years) exposed to repetitive brain trauma from head-banging, poorly controlled epilepsy, rugby, and boxing to the findings in 21 control subjects. She described argyrophilic, tau-positive cortical NFTs and neuropil threads strikingly arranged in groups around small intracortical blood vessels, in addition to diffuse granular cytoplasmic immunopositivity found in some neurons.[7] Geddes also noted that the topography of the pathology principally involved the depths of sulci and that the perivascular NFTs and neuropil threads were immunoreactive with a variety of monoclonal antibodies to p-tau, including AT8 (Ser 202/Thr205), AT180 (Thr231), and AT270 (Thr181). Notably, the hippocampus was normal in all autopsy cases, no Aß deposits were detected, and none of the age-matched controls showed similar perivascular tau pathology.[7]

Additional reports of CTE continued to trickle in; CTE was found in a 33-year-old achondroplastic dwarf who had worked for 15 years as a circus clown and participated in dwarf-throwing events, for example;[10] however, the disease was generally considered to be obscure. The case reports from Omalu and colleagues describing CTE in two former professional American football players in 2005 and 2006[11,12,26] marked the beginning of a turning point in the perception of CTE from a rare condition affecting boxers and isolated others to a neurodegeneration that could affect high-performance, popular, contact sport athletes.

In 2009, McKee and colleagues detailed the pathological and immunohistochemical findings in two former boxers and an American football player with CTE and systematically reviewed the previous 48 neuropathologically verified cases of CTE from the world's literature. The authors noted that 90% of the previously published cases of CTE affected athletes, principally boxers (85%) and, more recently, football players (11%). Individuals with CTE tended to start their sport early (ages 11–19, mean 15.4 years); their first symptoms began at widely varying ages (25–76, mean 42.8 years); one third were symptomatic at the time they stopped playing the sport; and, in most, the disease progressed slowly for several decades (2–46, mean 18.6 years). Symptoms of CTE commonly included memory loss, cognitive decline, irritability, aggressive or violent behaviors, unsteadiness, headaches, and Parkinsonism; 30% had a prominent mood disturbance, which was usually depression; 41.2% had a movement abnormalities; dementia was frequent in individuals with long-standing CTE; and CTE was often misdiagnosed as AD.

Furthermore, McKee and colleagues detailed the full spectrum of the pathology and the regionally specific immunocytochemical abnormalities of phosphorylated tau in CTE. Of note, cavum septum pellucidum or septal fenestrations were common findings, present in 69% and 49% of CTE cases, respectively. Microscopically, neuronal loss and gliosis were common in severe cases, most pronounced in the medial temporal structures (amygdala, hippocampus, entorhinal cortex), frontal and temporal lobes, subcallosal and insular cortex, medial thalamus, hypothalamus, diencephalon, mammillary bodies, substantia nigra, and nucleus accumbens. Neuronal loss was usually, but not always, accompanied by severe neurofibrillary degeneration. Using whole mount landscape slides of the p-tau pathology, the authors emphasized the presence of astrocytic inclusions and dot-like and spindle-shaped neurites, structures that had not been observed previously. They also highlighted the regionally distinctive, irregular distribution of NFTs with multifocal dense patches in the superficial layers of the cortex and the prominent perivascular pattern.[13] The authors stressed the striking predilection for the depths of the cortical sulci in the frontal, temporal, insular, septal, and parietal cortices with sparing of primary visual cortex.[13,27] Furthermore, they noted the pathological involvement of the white matter, including the subcortical U-fibers, corpus callosum, and subcortical white matter.

In 2012, early changes of CTE were reported in a small series of young veterans of the Iraq and Afghanistan conflict exposed to explosive blast or repetitive concussion.[16–18] McKee and colleagues noted that the changes of early CTE in the young veterans were remarkably similar to the findings in young football players and other contact sports athletes as well as a rodent model of explosive blast injury.[17]

In 2013, the spectrum of p-tau pathology was described in the largest case series of CTE to date consisting of 68 male subjects with CTE, ranging in age from 17 to 98 years (mean 59.5 years); 18 age- and gender-matched individuals without a history of brain trauma served as controls. McKee and colleagues described unique tau pathology in CTE that was easily distinguished from other tauopathies, including AD. The distinctive features included perivascular foci of NFTs and astrocytic inclusions irregularly distributed in the cortex with a predilection for sulcal depths, foci of subpial p-tau astrocytes at the sulcal depths, and NFTs preferentially distributed in the superficial layers of cortex in areas away from the epicenters. In young subjects, including high school and college athletes, with the mildest forms of CTE, focal perivascular epicenters of NFTs and p-tau astrocytes clustered at the depths of the cortical sulci. In subjects with advanced disease, a severe tauopathy affected widespread

brain regions.[14] Other abnormalities included deposits of phosphorylated 43-kDa TAR DNA-binding protein (TDP-43) (80% of cases) that occasionally colocalized with p-tau, axonal dystrophy, and neuroinflammation.[14,27] McKee and colleagues proposed a staging scheme of progressive p-tau pathology consisting of four stages, stages I–IV (Figure 20.1), and preliminary criteria for the neuropathological diagnosis of CTE.[14] In former football players, they found a significant correlation between the stage of CTE pathology and the duration of football career, age at death, and years since retirement from football. These associations provided additional evidence supporting a direct association between trauma dose (as exposure-years) and severity of CTE as well as of progressive neurodegeneration over time.[14] By contrast, number of concussions, years of education, lifetime steroid use, and position played were not significantly related to CTE stage.

Older military veterans were also reported to have CTE.[14,18] Most veterans with CTE were also accomplished athletes, including professional and semiprofessional football players and professional boxers as well as amateur hockey and rugby players and a boxer.[14] Two veterans who developed severe CTE had experienced a moderate-to-severe traumatic brain injury (TBI) from assaults or motor vehicle accidents while in service (one intraparenchymal TBI with persistent, poorly controlled posttraumatic epilepsy, the other a spinal cord injury).[18]

Recently, as part of a National Institute of Neurological Disorders and Stroke (NINDS) and National Institute of Biomedical Imaging and Bioengineering (NIBIB) funded initiative, a panel of expert neuropathologists evaluated 25 cases of various tauopathies blinded to all clinical, demographic, and gross neuropathological information. The tauopathies included examples of CTE, AD, progressive supranuclear palsy, argyrophilic grain disease, corticobasal degeneration, primary age-related tauopathy (PART), and GPDC. A single laboratory processed all cases uniformly, and the resulting slides were scanned into digital images that were provided to neuropathologists blinded to all other information. The evaluating neuropathologists submitted their independent evaluations prior to a face-to-face meeting.

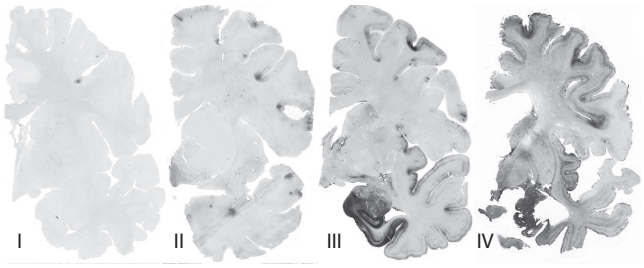

Figure 20.1 In Stage I CTE, isolated perivascular p-tau lesions are found in the cerebral cortex. In stage II CTE, multiple perivascular p-tau foci are found in the cerebral cortex. In the adjacent cortex, NFT are scattered throughout the superficial cerebral layers. In stage III CTE, confluent patches of NFT, neurites and p-tau filled astrocytes are found around blood vessels at the sulcal depths, and widely distributed throughout the cerebral cortex including the medial temporal lobe. By stage IV CTE, p-tau pathology is densely distributed throughout the cerebrum, medial temporal lobe structures, brainstem, cerebellum and occasionally, spinal cord (50 μm whole mount sections immunostained with CP-13).

The neuropathologists correctly identified CTE in 91.4% of their total responses and in 95.7% after the clinical information and gross neuropathological features were revealed. There was very good agreement between reviewers and CTE diagnosis (Cohen's kappa: 0.78) using the proposed criteria for CTE, indicating that CTE was reliably distinguished from other tauopathies by the provisional criteria.[14] The panel also made refinements and recommendations to the provisional criteria (Table 20.1). In addition, the panel determined that CTE has a pathognomonic lesion that distinguishes it from all other neurodegenerative diseases, including aging and nonspecific astrotauopathy (ARTAG).[28] The pathognomonic lesion of CTE is defined as an accumulation of abnormal tau in neurons and astroglia distributed around small blood vessels at the depths of cortical sulci and in an irregular pattern. The panel also agreed that p-tau immunoreactive dot-like structures were characteristic of the pathology, including the perivascular lesions. Moreover, the TDP-43-immunoreactive inclusions in CTE were considered to be distinctive from other neurodegenerations, and the pattern of hippocampal degeneration was unlike the typical pattern found in AD.[29] The group also defined supportive but nonspecific features of CTE, recommended a minimum blocking and staining scheme for pathological evaluation, and made recommendations for future study.

Gross pathology of CTE

Macroscopic changes are not seen in early-stage CTE but are typical of advanced disease. Macroscopic changes include reduced brain weight, cerebral atrophy (usually most severe in the frontal and anterior temporal lobes), enlargement of the lateral and third ventricles, cavum septum pellucidum, septal fenestrations, atrophy of the diencephalon and mammillary bodies, and pallor of the locus coeruleus and substantia nigra. Although cerebellar abnormalities were described in the initial reports of CTE affecting boxers, grossly identifiable cerebellar abnormalities are rarely present in CTE associated with other sports or activities.[14]

Hyperphosphorylated tau pathology in CTE

CTE is characterized by the deposition of hyperphosphorylated tau (p-tau) protein as NFTs, astrocytic inclusions, and dot-like neurites in the cortex around small vessels. The pathognomonic perivascular lesion shows a predilection for the depths of the sulci and is often associated with subpial collections of thorned astrocytes (Figure 20.2). The tau isoform profile and phosphorylation state are similar to AD,[30] and the neuronal p-tau pathology shows immunoreactivity to both three repeat (3R) and four repeat (4R) tau.[14,31] The

Table 20.1 Preliminary NINDS criteria for the pathological diagnosis of CTE

Required for Diagnosis of CTE

1. The pathognomonic lesion consists of p-tau aggregates in neurons, astrocytes, and cell processes around small vessels in an irregular pattern at the depths of the cortical sulci.

Supportive Neuropathological Features of CTE

P-tau-related pathologies:

1. Abnormal p-tau immunoreactive pretangles and NFTs preferentially affecting superficial layers (layers II–III), in contrast to layers III and V as in AD.
2. In the hippocampus, p-tau pretangles and NFTs preferentially affecting CA2 and CA4 in contrast from the preferential involvement of CA1 and subiculum in AD.
3. P-tau immunoreactive NFTs in subcortical nuclei, including the mammillary bodies and other hypothalamic nuclei, amygdala, nucleus accumbens, thalamus, midbrain tegmentum, nucleus basalis of Meynert, raphe nuclei, substantia nigra, and locus coeruleus.
4. P-tau immunoreactive thorny astrocytes in the subpial and periventricular regions.
5. P-tau immunoreactive large grain-like and dot-like structures (in addition to some threadlike neurites).

Non-p-tau-related pathologies:

1. Macroscopic features: Disproportionate dilatation of the third ventricle, septal abnormalities, mammillary body atrophy, and contusions or other signs of previous traumatic injury.
2. TDP-43 immunoreactive neuronal cytoplasmic inclusions and dot-like structures in the hippocampus, anteromedial temporal cortex, and amygdala.

Age-Related P-Tau Astrogliopathy That May Be Present, Nondiagnostic and Nonsupportive[28]

1. Patches of thorn-shaped astrocytes in subcortical white matter.
2. Subependymal, periventricular, and perivascular thorned astrocytes in the mediobasal regions.
3. Thorn-shaped astrocytes in amygdala or hippocampus.

Source: Adapted from McKee, A.C., Cairns, N.J., Dickson, D.W. et al. The first NINDS/NIBIB consensus meeting to define neuropathological criteria for the diagnosis of chronic traumatic encephalopathy. *Acta Neuropathologica*, 131: 75–86, 2016.

4R isoform of tau is predominant in astrocytes including the subpial p-tau astrocytic pathology.[14,31] 4R tau immunopositivity increases in prominence with age and disease severity.

Staging of p-tau pathology

The method of staging of p-tau pathology in tauopathies was adapted from the work of Braak and Braak who examined a series of 83 autopsy brains with AD for neurofibrillary changes and found a characteristic distribution pattern of NFTs and neuropil threads that permitted a differentiation of six stages.[32] This staging system now forms the basis for the neuropathological diagnosis of AD used by the National Institute on Aging,[33] and similar staging schemes are now in use for Aß plaques in AD[34] and Lewy bodies in Parkinson's disease.[35] In the examination of 68 cases of CTE, McKee and colleagues identified four pathological stages: stages I–IV[14] (Figure 20.1). In the earliest stage of CTE, stage I, p-tau NFTs and large dot-like and grain-like structures are found around small blood vessels as focal epicenters in the cortex (Figure 20.1). These perivascular foci have a tendency to be located at the sulcal depths of the frontal, temporal, parietal, insular, and septal cortices. In stage II CTE, there are multiple perivascular foci at the sulcal depths of the cortex, scattered NFTs in the superficial laminae of the adjacent cortices, and NFTs in the locus coeruleus and nucleus basalis of Meynert. In stage III CTE, confluent patches of p-tau immunoreactive neurons and astrocytes are found centered around blood vessels at the sulcal depths as well as in linear arrays in the superficial laminae of cortex. NFTs are also found in the hippocampus, entorhinal cortex, amygdala, substantia nigra, dorsal and medial raphe, and olfactory bulbs. Neurofibrillary degeneration in the hippocampus includes CA4 and CA2 as well as CA1. In CTE Stage IV, p-tau immunoreactive neurons and astrocytes are densely distributed throughout the cerebrum, thalamus, hypothalamus, mammillary bodies, basal ganglia, brain stem, cerebellar dentate nucleus, and occasionally, the spinal cord. There is often marked neuronal loss and gliosis of CA1 and the subiculum. Neuronal loss and astrocytosis may also be prominent in the frontal and temporal cortices associated with microvacuolation of layer 2. Primary visual cortex is generally spared.

Axonal pathology in CTE

Axonal injury, axonal degeneration, and white matter loss are constant features of CTE, and axonal injury most likely plays a critical role in initiating p-tau pathology. The degree of axonal dysintegrity generally parallels the severity of the disease. In early-stage CTE, stages I and II, scattered axonal varicosities are found in the deep layers of the frontal and temporal cortices, subcortical white matter, and deep

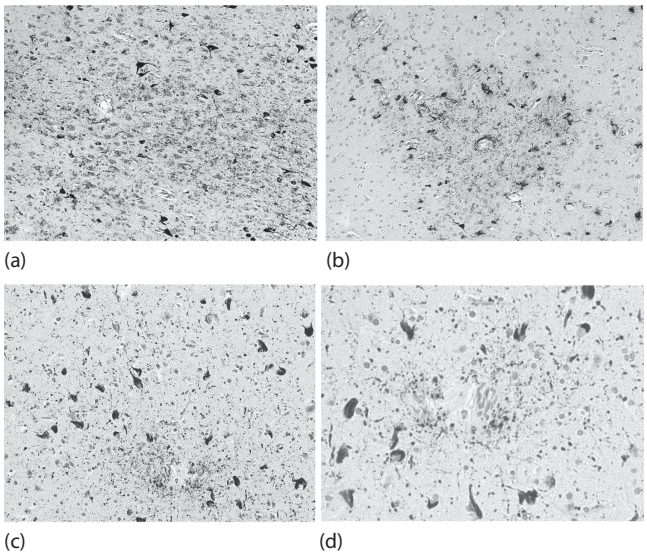

Figure 20.2 The pathognomonic lesion of CTE consists of an abnormal accumulation of p-tau in neurons, astrocytes, and dot-like structures around small vessels irregularly distributed at the depths of the cortical sulci. All images paraffin embedded 10-µm sections stained with AT8. **(a, b)** Magnified at 100×. **(c, d)** Magnified at 200×.

white matter tracts of the diencephalon and are occasionally immunoreactive for p-tau. In more advanced disease, stages III and IV, axonal loss is severe with frequent distorted axonal profiles in the cortex and subcortical white matter and widespread p-tau abnormalities in axonal tracts.

TDP-43 pathology in CTE

Most cases of CTE also show abnormalities for abnormally phosphorylated TDP-43 protein with positive neuronal and glial inclusions and large rounded and dot-like neurites that may colocalize with p-tau inclusions.[14,27] TDP-43 immunoreactivity is found in nearly all stage IV CTE cases, most often as TDP-43-positive rounded and threadlike neurites, intraglial and intraneuronal inclusions in cerebral cortex, medial temporal lobe, diencephalon, basal ganglia, brainstem and occasionally, spinal cord. In cases with severe TDP-43 deposition, dense accumulations of TDP-43 inclusions and neurites are found in all layers of the neocortex, particularly layer II, as well as occasional TDP-43-positive inclusions in the dentate fascia of the hippocampus, a distribution pattern that overlaps with the distribution of TDP-43 found in FTLD-TDP.[36]

Aß pathology in CTE

Unlike AD, CTE is a primary tauopathy, not a secondary tauopathy. In other words, the tauopathy of CTE appears first in the progression of disease and prior to the appearance of Aß plaques. Aß containing plaques are present in 52% of individuals with CTE, primarily as diffuse Aß plaques;[37] Aß plaques are not found in early-stage disease. In CTE, Aβ plaques are significantly associated with accelerated tauopathy, Lewy body formation, dementia, Parkinsonism, and inheritance of the ApoE4 allele.[37] In contrast, Aß deposits are essential to the diagnosis of AD and are present even in early stages of AD.[38]

CTE as a comorbidity in neurodegenerative disease brain banks

Using the newly devised NINDS criteria, Bieniek et al. reviewed the clinical records and brains of 1,721 cases donated to the Mayo Clinic Neurodegenerative Disease Brain Bank over the past 18 years and found 32% of contact sport athletes had evidence of CTE pathology.[39] No cases of CTE were found in 162 control brains without a history of brain trauma or in 33 cases with a history of a single TBI. Of the 21 athletes with CTE pathology, 19 had participated in football or boxing, and many were multiple sport athletes, including rugby, wrestling, basketball, and baseball. One athlete played only baseball, and another athlete only played basketball. Similarly, Ling and colleagues screened 268 cases of neurodegenerative diseases and controls and found CTE changes in 11.9%. Of the cases with CTE, 93.8% had a history of TBIs; 34% had participated in high-risk sports; including rugby, soccer, cricket, lacrosse, judo, and squash; and 18.8% were military veterans.[40]

CTE with ALS

Approximately 10% of individuals with CTE develop a progressive motor neuron disease that is characterized by profound weakness, atrophy, spasticity, and fasciculations and fulfills criteria for the clinical diagnosis of ALS.[14,27] In addition, a recent screen of ALS cases from the Mayo Clinic Jacksonville ALS brain bank and the Boston VA ALS brain bank found that 6/91 (6.6%) and 5/113 (4.4%) cases, respectively, had pathological features of CTE (all Caucasian males).[41] Most individuals with CTE and ALS present with symptoms of ALS and develop mild cognitive and behavioral symptoms several years after the onset of motor weakness and fasciculations. Individuals with motor neuron disease and CTE tend to die from respiratory failure at younger ages and in earlier stages of CTE (stages II–III) compared to CTE subjects without ALS. Approximately one third of CTE + ALS subjects present with depression or behavioral or cognitive changes related to CTE many years before developing ALS symptoms and are diagnosed with CTE, grade III or IV, and ALS at autopsy. Subjects with CTE + ALS show more severe TDP-43 pathology than subjects with CTE alone. The marked accumulation of pTDP-43 aggregates in advanced stages of CTE, the partial immunohistochemical colocalization of p-tau with pTDP-43, and the development of ALS and FTLD in some individuals with CTE suggests that CTE and FTLD share some pathogenic mechanisms.[42,43]

Pathological distinctions between CTE and AD or aging

Recently, there have appeared a number of reviews, editorials, and commentaries that have argued that there is no credible evidence that CTE exists and that the pathology of CTE has been confused with the effects of aging, AD, or a type of FTLD.[44–49] The findings of the NINDS consensus meeting are at odds with these statements as the panel was able to easily distinguish CTE from age-related tauopathy, AD, argyrophilic grain disease, corticobasal degeneration, and progressive supranuclear palsy as well as GPDC. The p-tau pathology that develops with aging shares no microscopic features with CTE even in the mildest stages. In CTE, cortical sections show a distinctly irregular distribution of p-tau pathology and a prominent perivascular distribution with an accentuation at depths of sulci. The hippocampus and entorhinal cortex are free of pathological p-tau changes in early-stage CTE. The p-tau pathology that develops in aging is never perivascular, is primarily neuronal, is most severe in the entorhinal cortex and hippocampus in early disease, and shows no proclivity for the subpial region or sulcal depths.[50] The p-tau pathology found in CTE also substantially differs from that found in AD. In AD, the cortical distribution of NFTs is diffuse, not irregular; preferentially involves laminae III and V (not layers II–III); and there is no clustering of neurofibrillary pathology perivascularly, at sulcal depths, or in the subpial regions. Most importantly, neuritic and diffuse Aß plaques are a necessary diagnostic feature of AD whereas only half of all cases of CTE show Aß plaques, and they are never a feature of early stage CTE.

As well, the question of controls is often cited as a failure of previous neuropathological investigations despite the fact that controls have been reported to be negative for CTE pathology in multiple studies. Geddes and colleagues reported the lack of the findings of CTE in 21 age-matched subjects with no history of neurotrauma.[7] McKee and colleagues reported the lack of CTE in 18 age- and gender-matched control subjects,[14] and Bienek and colleagues reported the absence of CTE changes in 162 control cases from the Mayo Clinic Jacksonville brain bank without a history of brain trauma.[39]

CLINICAL SYNDROME

The current understanding of the clinical presentation of CTE suggests that it presents in one or more of three distinct domains: mood/behavior, cognitive, and motor. Key mood features include depression, irritability, and hopelessness with additional symptoms, such as anxiety, agitation, and apathy.[14,51–53] With regard to behavior, early symptoms often include explosivity and aggression; poor impulse control; poor insight; paranoid ideations; risky behavior; disinhibition; inappropriate sexual behavior; and verbal, physical, and substance abuse.[14,51–53] Cognitively, the most prominent deficits tend to be in memory and executive functioning. Other cognitive symptoms include poor concentration, judgment and problem solving, language and visual spatial deficits, and, in advanced stage cases, dementia.[14,51–54] Motor symptoms including dysarthria, dysphagia, coordination problems, and Parkinsonism (tremor, decreased facial expression, rigidity, and gait instability) have also been reported,[52] potentially reflecting midbrain damage to motor tracts from concussive injury. Chronic headaches are common in individuals with CTE; the headaches often have migrainous features.[53]

Recent and past literature has proposed two distinct types of clinical presentation with regard to both domain and temporality of symptoms.[22,24,53] Stern and colleagues' recent review of cases with neuropathologically confirmed CTE distinguished between two courses of clinical presentation.[53] The first course initially presents with mood and behavioral symptoms earlier in life (mean age of 35 years) and progresses in severity to include cognitive symptoms later in the disease course. The second course presents with cognitive symptoms later in life (mean age of 60 years) and often progresses to also include mood and behavioral symptoms.

Clinical diagnosis of CTE

Like most neurodegenerative diseases, the definitive diagnosis requires neuropathological examination of brain tissue. Several groups have proposed preliminary and/or research diagnostic criteria for the clinical diagnosis of CTE.[54–56] Current proposed criteria follow a similar structure to that of other neurodegenerative diseases, such as the National Institute on Aging—Alzheimer's Association clinical diagnostic criteria,[57] which differentiate between possible and probable diagnoses based on the endorsement of various clinical symptomology. The most recent criteria proposed by Montenigro et al.[54] dichotomizes between the pathological diagnosis of CTE, which is reserved for postmortem diagnosis only, and the establishment of the clinical syndrome of CTE during life, referred to as traumatic encephalopathy syndrome (TES).[54] The TES syndrome is further dichotomized into several potential subtypes based on the presence or absence of various clusters of symptoms, including behavioral/mood variant, cognitive variant, mixed variant, and TES dementia (for a full review see Montenigro et al.[54]). These updated criteria represent an important advancement, and their utility in both research and clinical settings in differentiating CTE from other pathologies with a high degree of sensitivity and specificity is in the process of being validated.[58]

The use of *in vivo* biomarkers will contribute to the utility and accuracy of clinical diagnosis. Although there are no currently available diagnostic biomarkers, many promising techniques are being developed and tested. Data on novel tau-specific PET ligands have demonstrated encouraging results,[59,60] and studies utilizing diffusion tensor imaging (DTI) have also showed the capability to detect changes to white matter integrity following head trauma.[61,62] Additionally, functional connectivity (fMRI) and other advanced imaging measures of axonal integrity, such as

magnetic resonance spectroscopy (MRS) to detect biochemical metabolites as well as CSF and plasma protein markers (including p-tau and total tau) are under development.[57,63,64]

If history is any guide, our understanding of the clinical diagnosis of CTE will follow a trajectory similar to other neurodegenerative diseases—that is, there will be intense scrutiny, debate, and revision before formal diagnostic clinical criteria are validated and agreed upon.[65] Frontotemporal dementia (FTD) and Lewy body disease took similar trajectories in the development and validation of key clinical symptoms as the symptoms overlapped with other well-studied neurodegenerative diseases.[66] Although a current criticism of the clinical presentation of CTE stems from the commonality of its symptoms with other neurodegenerative disorders, this is expected in the early stages of clinical research.

RISK AND PROTECTIVE FACTORS

There are many potential variables surrounding exposure to repetitive head impacts that might influence the risk for CTE later in life. The age at which athletes experience head impacts may influence CTE risk. Recent studies in retired NFL athletes indicate that exposure to football before the age of 12 is associated with greater cognitive impairment and more white matter abnormalities on MRI.[67,68] What other lifestyle factors might mitigate the risk for CTE remains to be determined. Chronic inflammation in combination with obesity, hypertension, diabetes mellitus, atherosclerosis, or heart disease may facilitate p-tau accumulation, spread, and neurodegeneration.[69–72] On the other hand, enhanced cognitive reserve might delay the development of clinical symptoms in CTE. Genetic variations are also likely to play an important role in modulating the relationships between exposure to head trauma, neuropathologic changes, and disordered cognition and behavior. A recent study indicated that a slight increase in *MAPT* H1 haplotype exists in subjects with sports exposure and CTE pathology compared to those without CTE pathology.[39]

Is CTE caused by trauma?

In trauma-associated human disease, no direct determination of causality can be ethically conducted. As such, the determination that needs to be made is whether the *preponderance* of the evidence allows one to *reasonably* conclude that the disease is associated with traumatic exposure. There is substantial evidence using animal models in support of the association.[17,73–96] Animal models have consistently shown that concussive or blast mTBI can lead to pathological changes in rodents and swine and that repetitive mTBI increases the severity of the pathological changes.[17,73–96] Goldstein et al. developed a model of blast neurotrauma and found that wild-type mice exposed to a single blast developed pathological changes consistent with CTE, including p-tau immunoreactivity, axonopathy, and widespread astrocytosis. The mice also demonstrated cognitive changes, including learning and memory deficits.[17] Huber et al. found that after a single mild blast, mice showed elevated levels of multiple phosphor- and cleaved-tau species in neurons. These aberrant tau species persisted for at least 30 days postblast, indicating that these species may play a role in the transition from acute response to trauma to chronic processes.[78] Kondo et al. found robust cis-tau pathology after experimental TBI in mice that was associated with disruption of axonal microtubules and mitochondrial transport and spread to other neurons with apoptosis at 6 months. Furthermore, an antibody to cis-tau appeared to halt the spread of the tauopathy.[97]

Animal models have also shown that repetitive neurotrauma leads to greater cognitive deficits and behavioral changes compared to single TBI. Prins et al. showed that rats exposed to repetitive mTBI showed an increase in axonal injury, astrocytic reactivity, and increased memory impairment compared to single mTBI mice.[89] In a study using h-tau mice, which express wild-type human tau isoforms on a null murine tau background, mice exposed to repetitive mTBI had significantly greater p-tau immunoreactivity compared to mice exposed to a single mTBI. Repetitive mTBI also resulted in an increase in astrocyte and microglia activation that was not found in the single mTBI mice.[96] This difference may be partly attributable to a period of enhanced vulnerability that follows the initial mTBI, in that a second impact delivered within a short window of time significantly worsens the clinical and pathological outcome. Longhi and colleagues showed that mice that sustained a second impact 3 to 5 days after an initial impact injury showed an exacerbation of cognitive deficits, axonal injury, and motor impairment. When the second impact was delayed for 1 week after the first concussive injury, the mice show no exacerbated deficits.[98] Prins and colleagues hypothesized that the temporal window of vulnerability is due to a prolonged period of impaired glucose metabolism that follows the initial injury. They showed that cerebral glucose metabolism decreases by 19% after a single mTBI in rats but returns to normal in 3 days. Rats that sustained a second impact during this 3-day period showed a 36.5% decrease in glucose metabolism whereas rats impacted 1 week after initial injury were nearly identical to rats that received only a single injury.[99] A similar vulnerable period after initial mTBI has been replicated in a number of other animal studies[100–104] and is postulated to occur in young athletes who experience second-impact syndrome (SIS).[15,105–107] Although further research is needed to identify the critical variables essential to the development of CTE after repetitive mTBI, including the role of genetics, inflammatory response, age, gender, and substance abuse to the neurodegeneration, the preponderance of the evidence supports the conclusion that CTE is directly associated with trauma. This is also consistent with the dose response found in football players with CTE: the longer the duration of exposure to football, the more severe the CTE pathology.

Contact sport athletes are especially susceptible to multiple subconcussive injuries experienced over short time

intervals. In a study of 37 amateur soccer players, the number of estimated headers was associated with white matter abnormalities and neurocognitive deficits after 1 year.[108] Significant white matter changes were also found in a cohort of professional nonconcussed soccer players when compared to cohort of nonconcussed swimmers.[62] American football players are routinely exposed to multiple subconcussive impacts with some high school and college athletes experiencing an excess of 1,000 subconcussive hits in a single season.[109,110] A single season of collegiate football at the Division III level was also found to be associated with white matter abnormalities that lasted up to 6 months after no-contact rest.[61]

BIOMECHANISMS OF CTE NEURODEGENERATION

Axonal injury, cytoskeletal disruption, metabolic derangement, microvascular injury, and neuroinflammation that occur after exposure to multiple mild TBIs most likely trigger a self-perpetuating pathological cascade leading to CTE in susceptible individuals. Linear and rotational, acceleration-deceleration forces cause the gelatinous brain to elongate and stretch; this distortion is greatest at the depths of the cerebral sulci of the brain and around the microvasculature. This tissue distortion produces multifocal injury to long filamentous structures in the brain, primarily the axons and small blood vessels, with multifocal blood–brain barrier loss. Traumatic axonal injury also results in alterations in axonal membrane permeability; ionic shifts, including massive influx of calcium; release of caspaces and calpains; hyperphosphorylation and mislocalization of the microtubule-associated protein tau. Under normal physiological conditions, tau is phosphorylated at a small number of sites and is localized to the axon where it binds to microtubules and stabilizes the cytoskeleton. Under pathological conditions, including after trauma, tau becomes hyperphosphorylated, dissociates from microtubules in the axon, and is displaced to the somatodendritic compartment in abnormal aggregates as NFTs.[111,112] Neuroinflammation, which occurs within minutes of a traumatic injury, can also promote tau pathology.[113] Cells at the injury site release cytokines and chemokines that lead to the recruitment of peripheral neutrophils and monocytes with simultaneous activation of resident astrocytes and microglia.[113] Acute metabolic disturbances also occur, including altered ionic flux, unregulated glutamate release, mitochondrial dysfunction, and oxidative stress.[114] Neurotoxic phosphorylated tau proteoforms, such as cis-tau, aggregate early after the trauma and continue to accumulate and spread in the brain long after the traumatic insult.[97] Furthermore, these oligomeric, abnormally truncated, and phosphorylated tau proteins extensively colocalize in the perivascular tau lesions that are the essential, diagnostic hallmark of early CTE.[115]

A unifying hypothesis in the pathogenesis of CTE would be that these abnormally phosphorylated tau proteoforms accumulate at the stress points of the trauma, i.e., at the depths of the cortical sulci and around small vessels. These isolated focal p-tau aggregates are pathologically evident as the *pathognomonic lesions* of CTE (stage I CTE) and are associated with neurotoxicity and neurodegeneration. Repetitive traumatic injury causes additional pathognomonic lesions to develop in multiple foci (stage II CTE). Cumulative accumulation of p-tau eventually builds to a critical threshold that overwhelms recovery mechanisms and triggers a widespread neurodegenerative process. At this point, even in the absence of further trauma, the accumulation of p-tau aggregates has reached a level that promotes continued accumulation and spread continued through the nervous system through a variety of mechanisms, including possibly protein templating mechanisms of transneuronal and transynaptic propagation,[116] tau secretion,[117] and extracellular cerebrospinal fluid (CSF) clearance via the glymphatic channels.[118] Neuroinflammation associated with the initial repetitive trauma and further aggravated by the accumulation of toxic p-tau fragments may exacerbate the neurodegeneration. The progressive neurodegeneration results in widespread p-tau accumulation in the cortex, medial temporal lobe (hippocampus, amygdala, and entorhinal cortex), and deep nuclei (including the nucleus basalis of Meynert, substantia nigra, locus ceruleus, and others).

Tau propagation in the CNS

Converging evidence from human, animal, and cultured cell studies indicate that tau interacts with membrane components to facilitate a self-perpetuating prion-like propagation.[116,119–122] In this model, fibrillar tau aggregates are released into the extracellular space where they are subsequently taken up by a recipient cell by micropinocytosis.[123] Direct contact with the recipient cell's natively folded tau protein results in templated misfolding and toxic amplification.[116,119,124–127] Studies using wild-type mice injected with tau inclusions extracted from human subjects who died from various tauopathies (i.e., argyrophilic grain disease, progressive supranuclear palsy, corticobasal degeneration) develop pathologic lesions characteristic of the respective disease of origin.[128] In a self-perpetuating manner, tau pathology spreads along established networks of synaptic connectivity in the brain.[129] Although phosphorylation and misfolding of tau is initially a reversible process,[130,131] similar to the self-limited nature of most concussive injuries and postconcussion syndromes, toxic tau seeding and propagation can promote further neuronal loss and neurodegeneration. When the individual first becomes symptomatic may depend on individual resistance and susceptibility factors that modulate compensatory responses to the pathology; however, with progressive accumulation and neurodegeneration, most individuals eventually develop symptoms.

Delayed onset of symptoms, often decades after the trauma exposure, is characteristic of 70%–80% of individuals with CTE.[13] Factors that potentially influence the age at onset of symptoms might include disease location (i.e., perivascular p-tau lesions in symptomatically sensitive regions,

e.g., amygdala, perirhinal cortex, prefrontal cortex, dorsolateral superior frontal cortex, etc.); differences in secondary modulating factors, such as neuroinflammation; and resiliency factors, such as cognitive reserve. Typically, if an individual becomes symptomatic with stage II CTE lesions, the symptoms that emerge are those of behavior and mood disorders. Perhaps, if the disease develops more slowly or the early lesions do not involve symptomatically sensitive brain regions or the individual is more resilient, symptoms do not appear until the disease has reached stage III disease when p-tau neurofibrillary degeneration involves widespread cortical and subcortical structures, including the hippocampus, amygdala, and entorhinal cortex and is clinically evident as memory impairment and executive dysfunction. This would explain the age discrepancy between individuals who present as behavioral or mood disorders (stage II disease; average age 35 years) and individuals who present as memory or executive dysfunction (stage III disease; average age 54 years).[53]

Other pathogenetic considerations

Other pathologies that contribute to CTE include microvascular injury and blood–brain barrier (BBB) disruption. The BBB is comprised of a network of capillary endothelial cells joined by tight junctions, surrounded by basal lamina, pericytes, and astrocytic perivascular end feet. Astrocytes provide the cellular link to the neurons.[132] After a single season of play and in the absence of overt concussion, American football players were found to have imaging evidence of BBB disruption thought to be the result of exposure to "subconcussive" impacts.[133] BBB disruption has also been found after blast injury.[134] In addition, 47% of late survivors of a single moderate-to-severe TBI were reported to have multifocal, abnormal, perivascular, and parenchymal fibrinogen and immunoglobulin G deposits in the cerebral cortex, suggesting that widespread BBB disruption may persist years after the traumatic insult.[135]

There is also monocyte infiltration of the brain parenchyma via the leptomeninges after TBI. Acute TBI induces vascular damage, meningeal cell death, and the generation of reactive oxygen species (ROS) that ultimately breach the glial limitans and promote spread of the injury into the parenchyma. In response, the brain elicits a neuroprotective inflammatory response characterized by meningeal neutrophil swarming and microglial reconstitution of the damaged glial limitans.[136]

Neuroinflammation has both beneficial and detrimental effects on the brain and spinal cord tissue.[137,138] Comprising 12% of cells in the brain, microglia represent the primary resident immune cells of the CNS.[138] In their usual resting state, microglia are highly dynamic and continuously survey and maintain the brain's microenvironment with motile processes and protuberances.[139] After minor neurotrauma, microglia become chronically activated and hypervigilant with the development of an amoeboid or jellyfish-like morphology.[136] The reactive microglia secrete proinflammatory cytokines and form honeycomb networks that provide structural support to the injured meninges and parenchyma[136] as well as phagocytic jellyfish microglia to eliminate cellular debris.[140,141] Concurrently, peripheral monocytes invade the brain parenchyma through the damaged meninges. This initial inflammatory reaction to brain injury appears to limit the extent of the injury;[142] however, chronic activation of this pathway might enhance neurodegeneration.

The CSF plays a role in fluid exchange with the brain's interstitial fluid (ISF) serving as a sink for interstitial solute[143] via a system termed the "glymphatic" channels. Using *in vivo* laser microscopy techniques and a radioactive tracer, Iliff et al.[143] demonstrated that subarachnoid CSF enters the parenchyma rapidly through paravascular spaces surrounding penetrating arteries; the fluid is subsequently cleared through large paravenous drainage pathways. Impairment of the glymphatic channels after TBI promotes the accumulation of exogenous tau around vessels.[118] Although this accumulation of tau around vessels is transient in mice, it remains to be determined whether disruption of the glymphatic flow contributes to the perivascular accumulation of tau in CTE.

SUMMARY

CTE is a latent neurodegeneration associated with repetitive concussive and subconcussive injury. There are usually many years between exposure to brain trauma and the development of clinical symptoms of CTE. Pathologically, CTE begins as isolated perivascular foci of p-tau deposits in neurons and astrocytes in the cerebral cortex (stage I CTE). These initial CTE p-tau lesions accumulate at the stress points of the traumatic forces, i.e., at the depths of the cortical sulci and around small vessels and are associated with focal neurodegeneration. Repetitive traumatic injury causes the production of additional perivascular p-tau lesions in multiple foci (stage II CTE). Individuals with stage II CTE often show behavior and mood changes. It is hypothesized that if a critical level of p-tau accumulates, it may trigger a feed-forward process of continued accumulation and toxic spread throughout the nervous system even in the absence of further exposure to trauma. This spread may involve protein templating mechanisms of transneuronal and transynaptic propagation, tau secretion, and extracellular CSF clearance pathways involving the glymphatic channels. Neuroinflammation associated with the initial trauma and aggravated by the accumulation of toxic p-tau fragments might exacerbate the neurodegeneration. As CTE advances, hyperphosphorylated tau deposits are found in widespread cortical regions as well as in the medial temporal lobe structures (hippocampus, amygdala, and entorhinal cortex) and in the deep nuclei (including the nucleus basalis of Meynert, substantia nigra, locus ceruleus, and others; stage III CTE). Individuals with stage III CTE often experience memory loss and executive dysfunction. Continued p-tau accumulation and spread result in stage IV disease; individuals with stage IV CTE are almost always demented.

As CTE is a slowly progressive neurodegeneration, there is great promise that early therapeutic intervention would be effective. Successful treatment will require the development of methods to definitively detect focal CTE lesions during life—when the initial perivascular aggregations of p-tau are just beginning to develop. Positron emission tomography using p-tau ligands and blood biomarkers look encouraging as methods for early *in vivo* detection. Finally, there is great hope for the development of therapies that would limit p-tau accumulation and spread and thus interfere with further decline in subjects already exposed to traumas and at high risk for chronic neurodegeneration.

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Posttraumatic epilepsy and neurorehabilitation

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INTRODUCTION

Two percent of patients with traumatic brain injury (TBI) experience early seizures, defined as occurring while the patient is still suffering from the direct effects of the head injury, usually within the first 24 hours of injury although up to 2 weeks later in those with severe head trauma.[1] There is a 3.6-fold increase in late seizures (after the acute effects of head trauma have resolved). The majority of these late-occurring seizures occur in the first 2 years following TBI[2], although some increased risk continues for years, even decades, after the trauma.[3] Although epilepsy, i.e., late-occurring seizures, has long been recognized as a common sequela to brain injury, progress in understanding the underlying process by which posttraumatic epilepsy develops from an insult and effective treatments to alter this development have remained somewhat limited. Therefore, clinicians have little information regarding appropriate treatment of posttraumatic epilepsy, and as a result, its treatment has remained empirical and arbitrary. The decision to initiate or withhold antiepileptic drug (AED) therapy has far-reaching implications for rehabilitation of the traumatic brain-injured patient. Inappropriate use of anticonvulsants may cause unnecessary cognitive impairment in those persons not requiring medication. At the same time, experimental data suggest that certain types of seizures may retard functional improvement during recovery from brain injury, and other types have no deleterious consequences. Thus, it is crucial to differentiate patients who will require and benefit from AED therapy from those who will not.

EVALUATION OF EPISODIC BEHAVIORAL CHANGES

Episodes of abnormal behavior occur commonly after severe head injuries and present a diagnostic challenge for the treating physician. There are many potential etiologies for these episodes; therefore, it is crucial to determine the correct diagnosis in order to select the most appropriate and efficacious therapies to avoid iatrogenic complications. Several disease entities result in fluctuations of mental status in the posttraumatic brain-injured state. These include posttraumatic encephalopathy, seizures, postictal state, and numerous encephalopathies of toxic and metabolic etiologies. Episodic dyscontrol and disinhibition from frontal injury may occur. Altered sleep–wake cycles may lead to daytime somnolence, sometimes presenting as paroxysmal sleep attacks. The encephalopathy caused by the posttraumatic state is discussed in detail by Gelber elsewhere in this volume. Mentation and attention tend to fluctuate in the TBI patient and may be mistaken for seizures, especially when there is a superimposed encephalopathy of another etiology. Simple staring spells are rarely due to seizures in the setting of TBI. Nonepileptic spells (psychogenic seizures) and misinterpretation of behaviors by caregivers may be difficult to differentiate from epileptic seizures. Metabolic encephalopathies are characterized by fluctuating mentation and may also be mistaken for seizures. Inappropriate use of AEDs in these situations will not only be ineffective, but may result in worsening of confusion or agitation.

There are many common etiologies for acute encephalopathies. Medication-induced encephalopathies rank among the most common and easily remedied causes of confusional states. As a result of the brain injury, TBI patients possess a lower tolerance to the central nervous system (CNS) side effects of psychotropic drugs and other medications. Antihistamines and many over-the-counter preparations with anticholinergic properties are poorly tolerated and are often overlooked as causes of transient or prolonged confusion. Several centrally acting sedatives, especially benzodiazepines and barbiturates, have extremely long half-lives. From a pharmacokinetic standpoint, long half-lives result in a greater interval before steady state is achieved; thus, adverse effects on the CNS may not be apparent until several days after the start of medications, and cause and effect may not be apparent. As a general rule, sedative agents (including benzodiazepines, opioids, and barbiturates) exacerbate encephalopathies; therefore, they frequently aggravate confusion or agitation in TBI patients and should be avoided. Other drugs commonly used in the TBI patient may have profound effects on the CNS. The medication list should always be reviewed for histamine antagonists (e.g., cimetidine) and narcotics for the possibility that they are inducing the confusional state.

Several systemic derangements are commonly associated with the posttraumatic state. Head injury may cause the syndrome of inappropriate antidiuretic hormone (SIADH) and result in hyponatremia, which, in turn, may cause confusion. Systemic infections are common in the TBI patient because of reduced mobility and presence of indwelling catheters. Any infection may manifest as an abrupt decline in mental status or agitation. An acute decline or fluctuation in mental status may herald a pulmonary, urinary tract, or wound infection. In patients with open head injuries and skull fractures, the possibility of a CNS infection should always be considered when there is an abrupt decline in mental status. When in doubt, a lumbar puncture must be performed after careful assessment for potential causes of increased intracranial pressure. Hypoxia may also cause agitation and confusion and is commonly caused by pulmonary emboli from deep venous thrombosis or fat emboli. Stroke is usually not a cause of global cognitive dysfunction except in cases of multifocal, brain stem, or diencephalic strokes.

Syncope (fainting) may be confused with seizures, especially if there is associated tonic posturing. This entity is also called convulsive syncope. As the patient loses consciousness, there is dimming of vision, and the patient appears pale and clammy. The patient generally falls limply to the ground or slumps over if sitting. Occasionally, a brief tonic or tonic–clonic seizure occurs, adding to the confusion regarding the diagnosis. In contrast to epileptic seizures, the patient with a syncopal episode generally regains consciousness and orientation rather quickly. Medications such as tricyclic antidepressants, beta-blockers, and neuroleptics may result in systemic hypotension and lead to syncope.

Panic disorder may mimic epilepsy and is frequently seen in patients after trauma. Panic episodes may be mistaken for focal seizures with dyscognitive changes because of altered consciousness that may occur. Panic episodes and other spells of psychogenic etiology are often misdiagnosed as medically intractable seizures, and these diagnoses should be considered in patients who are not responsive to antiepileptic medications. A careful history will help sort out this differential diagnosis. Typically, in the case of a panic attack, the patient complains of feeling dissociated, smothered, and in need of fresh air. The patient may have perioral numbness, tingling of digits, and a feeling of impending doom. Generally, full awareness of surroundings is retained, and the patient is able to maintain conversation. Episodes of syncope may occur in patients with panic disorder. They are usually brief and vasovagal in nature. As opposed to patients with complex partial seizures, those with syncope due to panic attacks generally retain full awareness and can maintain a conversation until there is loss of consciousness. AEDs are ineffective for panic disorder whereas alprazolam and imipramine are very effective.[4]

CLINICAL EVALUATION OF SEIZURES

Seizures should be considered when episodes of discrete and stereotypic behaviors occur with or without altered or lost consciousness. Although an electroencephalogram (EEG) is often supportive, the diagnosis of epilepsy must be made on clinical grounds. The patient may provide only a vague or incomplete history, and the diagnosis often depends on a careful history taken from observers. Seizures are distinct, stereotyped episodes with a definite start and end. With the exception of status epilepticus, seizure usually lasts only a few minutes. Most seizures associated with TBI are focal onset seizures, occurring within limited cortical networks that have been damaged. Depending on the anatomy of TBI, seizures may or may not be associated with dyscognitive changes (for example, focal motor seizures involving only the motor networks without further spread). When abnormal electrical activity involves other parts of the brain, additional manifestations, including altered thought, cognition, or awareness, may occur. Bilateral involvement causes generalized seizures. Afterward, mentation will often clear within a few minutes with return to baseline, although postictal somnolence may persist. Prolonged confusion of hours to days is rarely caused by seizures and should alert the clinician to the possibility of other causes outlined above. Directed aggression is not seen during seizures or the postictal state although confusion and undirected aggressive behaviors may be seen.

Revisions[5] were made in 2010 to the classification of seizures and epilepsy to augment utility in both clinical care and research. The use of the terms *focal* and *generalized* is restricted to description of seizure types and not the epilepsy itself. The authors sought to redefine these seizure types with reference to networks against the older concept of discrete anatomical regions. The current recommendation

is to describe focal seizures further according to their motor, sensory-experiential, autonomic, or cognitive manifestations. The terms *simple partial* and *complex* have largely been abandoned as well as *grand mal* and *petit mal*. Secondary generalization from a focal seizure is important to distinguish from a generalized-onset seizure.

The distinction in seizure onset has important implications for the pathophysiology and therapy of the seizure. AEDs tend to be selective for the seizure type and are analogous to cardiac antiarrhythmic drugs, which are fairly selective for arrhythmia type. The behavioral manifestations of posttraumatic seizures relate to area of onset, usually in the penumbra of injury. Thus, injuries to the convexity of the brain often result in sensory or primary motor manifestations at seizure onset, such as migrating paresthesias or twitching and jerking of an extremity. Seizures of the temporal lobe may result in psychic phenomena, such as a sensation of fear or deja vu, followed by automatisms whereas frontal seizure foci often result in aversive motor or more complex behaviors.

During typical focal seizures with dyscognitive phenomena (previously called complex partial seizures), the patient will often stare and become nonresponsive or poorly responsive to commands. Automatisms frequently occur and take the form of lip smacking and swallowing or chewing (oral-alimentary automatisms) and fidgeting with objects. Although the patient may spontaneously speak or seem to respond to commands, the language is inappropriate to the situation. The patient may affirm or disagree when questioned but, generally, gives little more than simple responses and does not follow complex commands. Generally, combativeness occurs only when the person is restrained. Thus, when directed aggression occurs, such as seeking out and striking a staff member, the episode most likely is a conscious act and not the result of a seizure. Thereafter, there is often a several-minute period of confusion and disorientation, which represents the postictal state. The patient will often feel tired or exhausted and will frequently go to sleep. When present, a history of postictal confusion and lethargy often helps to identify episodes as seizures as they generally do not occur or are brief with spells of other etiologies. Amnesia for the event is often noted in patients with focal seizures affecting the memory networks, particularly the temporal lobes. Seizures emanating from the frontal lobes are often brief and may be confused with nonepileptic events due to the bizarre nature of the seizures reported, occasionally without impaired consciousness and without a period of postictal mental change.

In TBI patients, convulsive seizures result from secondary generalization, i.e., spread of the seizure from the seizure focus at the site of trauma to other parts of the brain, especially the brain stem, which appears to moderate the initial tonic phase of the convulsion.[6] Thus, the tonic–clonic episode often begins as a brief focal seizure with or without dyscognitive phenomena. The warning, or "aura," that patients often describe is actually the beginning of a seizure that is perceived while the person is conscious and is actually a focal seizure.

Tonic–clonic seizures occur as a result of generalization and consist of two phases: the tonic phase and the clonic phase. These phases are easily identified with a careful history. During the tonic phase, there is a sudden stiffening of all extremities. The epileptic cry may occur during this phase as a result of sudden diaphragmatic contraction. After a brief period, the extremities become tremulous. As the tremor slows in frequency, it evolves into a rhythmic jerking motion, the clonic phase. As the seizure ends, the jerking slows and ceases. After a tonic–clonic seizure, the person is invariably groggy and disoriented for several minutes. A recent monograph by Lüders et al.[7] is a useful reference for defining the clinical semiology of seizures.

Acute medical management is similar for both partial and tonic–clonic seizures. If semiconscious, the patient should be gently directed away from harm. During a convulsion, the patient should be rolled to one side to avoid aspiration if vomiting occurs. Contrary to common belief, the tongue cannot be swallowed or bitten off, and objects should never be forced into the patient's mouth. Insertion of hard objects, such as spoons or "bite sticks," may break teeth and cause serious complications of fragment aspiration and pneumonia. A soft oral airway may be used if it is easily inserted. If available, oxygen via face mask may be provided as well as suction if needed.

Epilepsy, by definition, consists of a tendency for recurrent seizures. As with seizures, epilepsies have been classified. The 2010 report by Berg et al.[5] recommends that the classification of epilepsy be as specific as possible based on known etiology and organized around age of onset. Electroclinical syndromes including childhood and juvenile absence epilepsy, juvenile myoclonic epilepsy, and epilepsy with generalized tonic–clonic seizures alone commonly begin in childhood or adolescence and are usually idiopathic or genetic in etiology. These epilepsies are diagnosed by their distinctive patterns on the EEG, which consist of bilateral synchronous epileptiform patterns. Their onset in patients following TBI is highly unusual and should be considered coincidental. It is important to identify these epilepsy syndromes because generalized-onset seizures, especially absence and myoclonic seizures, do not respond to or may be worsened by medications used for focal onset seizures, such as phenytoin, carbamazepine, and oxcarbazepine.[8,9] It is important to note that epilepsy itself may result in trauma and TBI, and preexisting epilepsy should be considered in patients with TBI and primary generalized epilepsy.[10]

ETIOLOGIC CONSIDERATIONS

Risk factors for posttraumatic epilepsy have been examined in several population studies. However, it is difficult to resolve the relative risk of specific characteristics of injury, such as the presence of intracranial bleeding and depth of injury, because these markers tend not to be independent

variables. Nonetheless, World War II, the Korean War, and the Vietnam War have provided ample data on risk factors for posttraumatic epilepsy. Overall, the risk for epilepsy following nonmissile head injury was 24% in World War II[11] and 12% during the Korean War.[12] Interestingly, the risk of epilepsy following penetrating missile injury was about 35% for both World War II and the Korean War, but was much higher (53%) in the Vietnam War[13] and with incredible persistence.[14] The differences between studies on Vietnam War veterans and previous war veterans may relate to both improved care of head injury and differences in the nature of injuries. In particular, high-velocity rifles were used in combat and, when combined with improved surgical care, may have resulted in a greater percentage of survivors with epileptogenic lesions. TBI is an important source of morbidity in survivors of war-induced injury in the Iraq and Afghanistan wars, with blast injury being the most common type of injury in these conflicts. Unfortunately, it remains unclear as to the degree to which blast-induced TBI contributes to risk for posttraumatic epilepsy.[15]

Risk factors have also been studied in nonmilitary injuries. Albeit somewhat complicated in terms of exact risk and risk factors, there is evidence to support increased risk for posttraumatic epilepsy even after mild head injury.[3] Across all injury severities, there is an elevated incidence of 9.1 (per 100) with the numbers increasing relative to injury severity (4.4, 7.6, and 13.6 for mild, moderate, and severe, respectively).[16] These numbers are a bit higher than earlier studies showing incidence of posttraumatic epilepsy after moderate injury as 1.6% and 11.6% after severe injuries.[1] In a comprehensive review, Lamar and colleagues[3] provide clear evidence across multiple populations that seizure occurrence after the first week of injury is predictive of seizure recurrence and posttraumatic epilepsy. This is similar to early studies[17] showing that the risk of posttraumatic epilepsy was 8.58% higher for those individuals with early seizures and 3.43% greater for individuals with frontal or temporal lesions on CT. The degree of hypoperfusion in the temporal lobes as detected by single-photon computed tomography (SPECT) has also been correlated with posttraumatic epilepsy.[18] Also associated with the increased risk of posttraumatic epilepsy (+3.49%) was the presence of an EEG focus at 1 month. Technologies, such as diffusion tensor imaging (DTI), have made it possible to identify other potential risk factors for posttraumatic epilepsy related to structural changes[19] at the micro level although the exact utility of this or whether it may serve as a "biomarker" for posttraumatic epilepsy remains to be seen.[3]

The risk of posttraumatic epilepsy in the presence of an intracerebral hematoma was estimated at 21% in nonmilitary injuries.[1] However, Guidice and Berchou[20] found intracerebral hematomas not to be predictive of posttraumatic epilepsy. This may be due to the fact that CT scans were used routinely in all head-injured patients at their center. Brain contusion with subdural hematoma was predictive of posttraumatic epilepsy in a population-based study.[21] In one small series, the development of posttraumatic epilepsy was correlated with the presence of bone fragments on CT scan studies;[22] however, the scope of this study could not establish whether the risk of bone fragments was independent of injury severity. The type of skull fracture also tends to predict the likelihood of posttraumatic epilepsy. Greater risk occurs in patients with depressed skull fractures,[1] and linear convexity or basilar fractures carry an intermediate risk. Final risk factors for posttraumatic epilepsy that have remained constant across studies and populations include duration of coma,[1,3,20] genetic susceptibility to epilepsy,[23,24] and age.[3,21]

When the epidemiologic studies are viewed as a group, it appears that the severity of brain injury best predicts whether posttraumatic epilepsy will occur. Although there is debate on the relative risk of any single factor, it is likely that most identified risk factors are indicators of a high degree of brain injury rather than being specific etiologies. Furthermore, posttraumatic epileptogenesis is probably dependent on several pathophysiologic mechanisms, which may partially explain the large number of identified risk factors.

DIAGNOSTIC INVESTIGATIONS OF POSTTRAUMATIC SEIZURES

The evaluation of the first seizures in all adults is focused on determining the presence of possibly treatable CNS lesions and on defining the risk for recurrence with an EEG. There is evidence that supports the use of EEG brain imaging with CT or MRI as part of the routine neurodiagnostic evaluation of adults presenting with an apparent unprovoked first seizure. Laboratory tests, such as blood counts, blood glucose, electrolyte panels (particularly, sodium), lumbar puncture, and toxicology screening, may be helpful as determined by the specific clinical circumstances based on the history, physical, and neurologic examination, but there are insufficient data to support or refute recommending any of these tests for the routine evaluation of adults presenting with an apparent first unprovoked seizure.[25]

The EEG is a useful tool for evaluating patients with episodic behavioral changes. Interictal abnormalities, such as epileptiform spikes or sharp waves, are often present in patients with epilepsy. A difficulty arises in that interictal abnormalities are transient, much like the seizures they attempt to detect. Thus, a normal EEG does not exclude the possibility of epilepsy. Conversely, an abnormal EEG alone does not diagnose epilepsy. As outlined in subsequent sections, there are important consequences of AED therapy; thus, it is crucial that the TBI patient not be treated solely on the basis of EEG findings. The EEG does provide supportive evidence of a seizure disorder when it is clinically suspected, and its greatest utility lies in its ability to help identify whether the seizure onset is partial or generalized. Despite its limitations, the EEG is one of the most important tests in evaluating epilepsy as it provides electrophysiologic information that cannot be obtained from any other laboratory investigation.

For example, a retrospective study of EEG findings in patients with head injury revealed no predictive value of focal or generalized EEG abnormalities.[26] However, this study included all abnormalities and did not specifically assess the risk of epileptiform patterns. The EEG is valuable as a prognostic factor in persons who have already experienced a seizure. The interictal hallmark of epilepsy is the epileptiform spike or sharp wave. When well-formed and definite, focal spikes are predictive of seizure recurrence in both brain-injured patients[27] and in patients with seizures of unidentified causes.[28] Focal EEG findings 1 month following TBI were associated with an increased risk of subsequent epilepsy in a prospective study of risk factors following an early seizure.[17] When compared to routine EEGs, epileptiform activity was more frequent in EEGs performed after sleep deprivation in epilepsy patients with a history of head trauma. EEG following sleep deprivation may, therefore, be a useful adjunctive measure of evaluation if routine EEG is unrevealing.[29]

The value of prolonged EEG monitoring after TBI has been promoted as a means by which to detect subclinical seizures and even predict posttraumatic epilepsy.[30] Postinjury EEG assessment revealed that subclinical seizures occur frequently despite anticonvulsant drug administration.[30] As many as 22% of traumatically brain-injured individuals have postinjury seizures within the first 2 weeks,[30] many of which are subclinical. Postinjury EEG monitoring may help define the impact of seizure activity on patient outcomes, especially in regards to the risk for subsequent epilepsy. The utility of continuous EEG monitoring in detecting subclinical early seizure activity has also been found in children with posttraumatic seizures.[31]

The EEG study should follow the technical guidelines of the American EEG Society.[32] To briefly summarize, all studies should utilize at least 16 channels of EEG recording to allow for adequate spatial resolution and localization of EEG abnormalities. Gold disk electrodes should be used and attached to the scalp with either collodion or electrode paste to assure low electrical impedance. Needle electrodes should not be used because of their high impedance and the potential risk of blood–borne pathogens. Standard EEG montages should be used, per recommendations of the American EEG Society. Digital EEG recordings are now routinely obtained, which allows for reformatting the montages, if necessary. Drowsiness and sleep-enhanced expression of epileptiform abnormalities and recording during these stages of consciousness must be performed. The patient may be partially sleep-deprived during the night prior to the EEG study as this will increase the probability of recording epileptiform abnormalities and avoid the need for sedation.

There has been much debate over the advantages of special EEG electrodes used to improve the detection of interictal abnormalities. Nasopharyngeal electrodes are now rarely used. Standard scalp electrodes with high-distance electrode montages are as effective as nasopharyngeal electrodes at detecting epileptiform abnormalities and are considerably more comfortable.[33,34] Other scalp electrodes (such as T1 and T2 electrodes) increase sensitivity to temporal spikes.[35]

Prolonged EEG recording may be extremely useful in cases in which the cause of altered mental status episodes cannot be ascertained by conventional means, and the spells occur with enough frequency to be detected within the designated recording period. Twenty-four-hour ambulatory EEG monitoring is usually available at larger medical centers. These devices continuously record EEG and EKG activity for 1–2 days and may be performed on an outpatient basis. Nevertheless, there are several limitations to ambulatory recording. Artifact makes interpretation of ambulatory EEGs difficult, and technologists must review large amounts of data. As EEG technicians or other health care staff are not present to observe the recording, it may be difficult to later sort artifact from true abnormalities during playback. Moreover, if a diary is not carefully maintained during the recording period or the patient is unable to trigger the alarm on the recording unit reliably, it may not be possible to correlate the episodes in question with the EEG or EKG, or the episode may even be missed entirely.

Video electroencephalographic monitoring involves continuous recording of electroencephalographic, electrocardiographic, and other electrophysiologic data with simultaneous video recording of behavior. These studies allow precise correlation of behavioral changes with electrophysiologic data to determine the exact etiologies of the behavioral episodes. Such monitoring is costly and requires hospital admission. However, it may provide the only means to obtain definitive and conclusive information.

There has been recent interest in improving accuracy of localization of epileptogenic foci by noninvasive inverse localization using either EEG or magnetoencephalography (MEG). This technique may be preferable to invasive electrocorticography when resective surgery is being considered for medically refractory posttraumatic epilepsy.[36]

POTENTIAL EPILEPTOGENESIS ASSOCIATED WITH PSYCHOTROPIC MEDICATIONS

Behavioral and affective disorders are common after TBI, and it is often necessary to treat the brain-injured patient with psychotropic medications. Of concern is whether these agents lower seizure threshold. In high doses, tricyclic antidepressants induce seizures, but it is less clear to what extent they are proconvulsant at clinically effective doses. Many reports of tricyclic-induced seizures are retrospective and do not take into account the normal incidence of new onset seizures. When drug monitoring has been instituted to avoid high levels, the risk has been estimated at only 0.4%.[37] Although a 0.2% risk of seizures has been estimated for fluoxetine therapy on the basis of preclinical trials, fluoxetine is anticonvulsant in experiments using epileptic rodents with convulsive seizures.[38] A recent Cochrane database review concluded that there is limited existing evidence to inform the choice of antidepressant medications

in patients with epilepsy,[39] both with reference to their efficacy and safety and with reference to seizure exacerbation. Another recent, large, retrospective follow-up study, spanning patient data over 14 years, was conducted by researchers in Switzerland. This study reported an increase in risk of seizures among depressed patients with use of antidepressants of most classes (SSRIs and SNRIs) with the exception of tricyclic antidepressants (M. Blöchliger, meeting proceedings communication, 2015). Interestingly, an older, double-blinded placebo study has demonstrated imipramine to be effective adjunctive antiepileptic therapy in intractable atonic, myoclonic–astatic epilepsy and absence epilepsy in subjects without affective problems.[40,41] Thus, at nontoxic levels, tricyclic antidepressants may possess anticonvulsant properties for certain seizure types despite being proconvulsant at toxic levels. This bimodal response is frequently seen in other drugs with anticonvulsant properties, such as phenytoin and lidocaine.

The ability of tricyclic antidepressants to increase seizure frequency may be selective for seizure type. For example, a selective increase of tonic–clonic seizures may occur with use of imipramine or maprotiline in patients with mixed seizure types.[41] Neuroleptics are frequently utilized in the posttraumatic state for agitated behavior, and there are several reports of their proconvulsant effect. Unfortunately, little data exist on the actual risks of antidepressants and neuroleptics in the setting of TBI. However, from existing information on these agents, it appears that the actual clinical risk of seizure exacerbation by psychotropic medications is small and is usually far outweighed by the need to effectively manage a severe affective or disruptive state in the TBI patient. Thus, these medications should be used when necessary for psychiatric and behavioral problems. As a caveat, although the neuroleptics may not pose a risk for seizures after TBI, there are data showing that the administration of these drugs is detrimental to neurobehavioral recovery in this population.[42]

THERAPY FOR POSTTRAUMATIC EPILEPSY

It is common practice to initiate AEDs following acute TBI as prophylaxis against seizures. In acute treatment of severe brain injury, acute prophylactic treatment with AEDs, especially phenytoin and fosphenytoin, is common. Several studies have compared levetiracetam and phenytoin with respect to prophylaxis for early seizures following brain injury. The overall consensus seems to be that both drugs are equally efficacious when it comes to seizure prevention.[43] With fewer drug–drug interactions and a more favorable adverse effect profile, levetiracetam may become the preferred AED for acute TBI. Such treatment decreases the risk of early seizures but does not appear to prevent late-occurring seizures, that is, posttraumatic epilepsy. Studies on acute prophylaxis regarding the use of newer AEDs, other than levetiracetam, are lacking.[44,45]

Long-term prophylactic treatment with AEDs has not been shown to prevent subsequent development of posttraumatic epilepsy. As outlined in subsequent sections and based on a meta-analysis of anticonvulsant prophylaxis trials[46] as well as a Practice Parameter published by the American Academy of Neurology, there are clearly no firm data to justify long-term prophylactic AED therapy in TBI patients who have not experienced a late-occurring seizure.[45] Although some advocate prophylactic use of Mg++, a clinical trial failed to demonstrate efficacy of magnesium sulfate used acutely for protection from posttraumatic epilepsy.[47]

It is appropriate to treat those who experience late-occurring seizures, that is, posttraumatic epilepsy. Initiation of AED therapy should begin only after careful evaluation of the patient and seizures have been clearly identified. Almost all clinicians will begin therapy once two seizures have occurred, but there is debate on whether therapy should be initiated after the first seizure. A recent guideline published by the American Academy of Neurology advises that the risk of seizure recurrence following an unprovoked first seizure in an adult is about 21%–45% in the first 2 years. The risk increases in patients with a prior brain insult, epileptiform activity on EEG, a significant brain imaging abnormality, and a nocturnal seizure.[48] Selection of AED therapy must be based on several factors, including efficacy for seizure type and side effects. A specific AED may be quite selective for seizure type, thus necessitating seizure classification. Posttraumatic epilepsy is caused by focal or multifocal injury and, most often, is characterized by partial-onset seizures and secondarily generalized seizures. Accordingly, appropriate AED for posttraumatic epilepsy are those used for partial onset seizures. The most commonly used AEDs are listed in Table 21.1.

The effectiveness of AED in the treatment of epilepsy of all etiologies has been extensively examined with an emphasis on seizure control and tolerability. For example, in a British study involving patients with newly diagnosed partial-onset epilepsy comparing the efficacy of carbamazepine, phenytoin, and valproic acid, valproic acid exhibited the same efficacy as phenytoin and carbamazepine against partial-onset seizures and convulsion, suggesting its usefulness for these seizure types.[49] A Veterans Administration study compared the efficacy of carbamazepine to valproic acid for partial-onset seizures and indicated a modest but significantly lower efficacy of valproic acid against complex partial seizures.[50] Nevertheless, valproic acid appeared to be equally effective to carbamazepine against secondarily generalized tonic–clonic seizures. Because valproic acid is generally well tolerated, it should be considered for patients who are unresponsive or intolerant to carbamazepine. Kwan and Brodie[51] likewise have found that all carbamazepine, valproate, and lamotrigine had equal efficacy in newly diagnosed patients with epilepsy although tolerability differed. More patients on carbamazepine changed medication due to adverse events than those on the other two drugs.[51] A monotherapy trial comparing lamotrigine, gabapentin, carbamazepine, oxcarbazepine, and topiramate demonstrated that lamotrigine may be a cost-effective alternative to

Table 21.1 Guide to AED dosing and adverse effects

Medication/target dose (pediatric dose MG/KG/day)	Target serum levels	Idiosyncratic	Dose-related	Age-specific/other
Carbamazepine 1000–1200 (10–30 mg/kg/day)	4–12 μg/mL	Dermatologic (rash, including Stevens-Johnson), rare hematologic, hepatic	Vertigo, visual disturbance (diplopia), leukopenia	Hyponatremia in adults, leukopenia, liver induction, myoclonus in patients with generalized epilepsy
Gabapentin 1800–3600 (30–100 mg/kg/day)	4–20 μg/mL	Rash (rare)	Somnolence, irritability, weight gain	Renal excretion, no drug interactions
Lamotrigine 300–500 (1–15 mg/kg/day—dose depends on concomitant medication)	3–20 μg/mL	Rash, hypersensitive reaction	Ataxia, diplopia, GI, headache	Rash (1%–5% in children), Stevens-Johnson
Levetiracetam 1000–3000 (20–100 mg/kg/day)	5–50 μg/mL	None reported to date	Somnolence, ataxia	Agitation, aggression, depression
Oxcarbazepine 1200–2400 (15–45 mg/kg/day)	MHD—10–55 μg/mL	Rash (25% cross-reactivity with CBZ)	CNS, diplopia	Hyponatremia (3% of adults)
Phenytoin 200–400 (4–8 mg/kg/day)	10–20 μg/mL	Rash (5%–10%), hematologic, hepatic, lymphadenopathy others	Cosmetic, CNS, ataxia, nystagmus	Elevated LFTs, induction, reduced vitamin D, cerebellar degeneration
Topiramate 200–400 (5–25 mg/kg/day)	3–25 μg/mL	Rash (rare), acute glaucoma (rare)	Somnolence, memory disturbance, renal stones, parathesia	Language and cognitive disturbance (esp. polypharmacy), oligohydrosis
Valproic acid 750–1500 (20–60 mg/kg/day)	50–150 μg/mL	Hepatic failure, pancreatitis	Tremor, weight gain, alopecia, sedation and cognitive changes, thrombocytopenia, prolonged bleeding time	Hepatic failure (1/500 under age 2 on polypharmacy), elevated LFTs, GI upset with syrup, incidence of PCOS unknown, liver enzyme inhibition, teratogenicity
Zonisamide 200–600 (4–10 mg/kg/day)	10–30 μg/mL	Rash, hematologic, hepatic	Renal stones, anorexia, somnolence	Oligohydrosis in children, cross-sensitivity with sulfa drugs
Pregabalin 150–600 mg/day (no established pediatric dose)	None established	Edema, weight gain	Dizziness, sleepiness, ataxia, headache	Avoid abrupt discontinuation, also approved for pain Schedule V substance
Lacosamide 200–400	None established	Cardiac conduction abnormalities–AV block	Dizziness, headache, nausea, fatigue, ataxia, vertigo, diplopia, somnolence, nystagmus, prolonged PR interval	May cause elevations in liver enzyme values, minimal drug interactions

Note: For newer drugs, doses, levels, and adverse effects are based on reported clinical experience and not on adequate scientific information from clinical trials in most cases. Some medications do not have FDA approval for children. The package insert for each medication lists potential adverse effects, warnings, etc.

carbamazepine in treating partial seizures.[52] Levetiracetam, zonisamide,[53] and lacosamide have also been found to be effective in patients with focal epilepsy.[54]

All AEDs may cause significant problems with adverse effects, especially neurotoxicity, and pose problems for the TBI patient. Indeed, several AEDs commonly cause ataxia at high levels and may also exacerbate gait abnormalities at lower levels in some patients. This may present a problem to the patient who is returning to ambulation. There is a significant incidence of hyponatremia in carbamazepine-treated patients over the age of 25[55] as well as those on oxcarbazepine.[56] Postural tremor is a common side effect of valproic acid that may pose a problem to the TBI patient and can be particularly troublesome in patients who are prone to postural tremor. The tremor is reversible, dose-dependent, and responds to a dose reduction or other medications that block essential tremor (propranolol, primidone). Because the barbiturates, including phenobarbital and primidone, are poorly tolerated and result in a high incidence of cognitive impairment, they should not be used as first-line drugs but rather used in patients refractory to other antiepileptic medications. All AEDs carry the potential for cognitive impairment, and attention to the potential of their effects on CNS function is necessary.[57,58]

Newer AEDs (felbamate, gabapentin, lamotrigine, levetiracetam, lacosamide, oxcarbaxepine, pregabalin, rufinamide, vigabatrin, tiagabine, topiramate, zonisamide, perampanel, and ezogabine) have been approved by the Food and Drug Administration (FDA) since 1993. In general, they appear to have high therapeutic indices, i.e., a wide window between efficacy and toxicity, and have been demonstrated to be effective and safe in controlled studies. Improved pharmacokinetics provide an additional advantage of some of these newer AEDs, including renal clearance, the lack of significant protein binding, and the absence of CyP450 induction.[59] However, serious idiosyncratic adverse effects can occur. The use of felbamate has been restricted by the FDA for use in severe intractable epilepsy because of a significant risk of aplastic anemia estimated by the FDA to be 1:2,000. Lamotrigine is associated with a risk of serious rash in approximately 1:1,000 patients, usually at onset of therapy. Additionally, treatment-emergent side effects can be troublesome. For example, topiramate is associated with word-finding difficulties in some patients, particularly at higher doses or when the drug is used in polypharmacy. Gabapentin may cause weight gain and somnolence. Levetiracetam may cause behavioral side effects. Although monitoring serum drug levels, complete blood counts, and liver function are not required with most of the new AEDs (with the notable exception of felbamate), the difficulty in assessing clinical status of patients with significant traumatic encephalopathy may make such monitoring advisable. Practitioners should take advantage of published reviews of these drugs in textbooks and journals to familiarize themselves with their use.

In general, all AEDs should be introduced slowly to avoid problems with neurotoxicity, including somnolence and altered mental status. If introduced too quickly, carbamazepine may cause severe dizziness, and lamotrigine may precipitate a serious rash. However, when multiple seizures or status epilepticus occur, loading with phenytoin is often effective in controlling seizures. For intravenous use, fosphenytoin is better tolerated than phenytoin. Valproic acid is also available for intravenous use and can be used in relatively high doses, acutely, if necessary. Levetiracetam and lacosamide are also available for intravenous administration and appear to be well tolerated at therapeutic starting doses. The intravenous preparations of these drugs may be useful for patients who are unable to take oral medications, for instance, after surgical procedures. With all AEDs, clinical efficacy and tolerability determine appropriate dosing. Most of the newer AEDs do not have well-established therapeutic plasma levels, but nevertheless, the presence of significant traumatic encephalopathy may make determination of AED plasma levels appropriate. Drug plasma levels may be utilized to provide a rough guideline for therapy but should not be used as the sole indicator of therapy or toxicity.[60] It should be noted that plasma steady state is not achieved for up to seven half-lives of a medication so that levels are rarely useful acutely after dosing changes.

Phenytoin is unique among the commonly used AEDs in that it saturates binding sites at therapeutic levels, which results in zero-order kinetics. As a result of nonlinear kinetics, there is a proportionate increase in serum level at low doses of phenytoin, but at therapeutic levels, small increments result in marked elevations of levels.[61] In addition, phenytoin and valproic acid compete for protein binding, increasing the potential for dose-related toxicity and making routine measurements of phenytoin levels inappropriate when used in combination with valproate. Rather, unbound phenytoin levels should be obtained through reference laboratories as they are not routinely available in most hospital laboratories. Extended-release formulations of several AEDs are now available, including levetiracetam and valproate, allowing for once-a-day dosing, which may aid in adherence to dosing regimens.

The use of phenytoin, carbamazepine, and oxcarbazepine suspensions may be useful in patients who cannot swallow tablets or capsules. However, care must be taken to adequately shake the bottle before administering a dose to allow for even distribution of drug in the solution. Levetiracetam and lacosamide are available as solutions. Lamotrigine, levetiracetam, and zonisamide can be dissolved and given as a solution. Both valproic acid and topiramate are available as sprinkle capsules, but they cannot be given through gastric tubes due to the tendency of the sprinkles to adhere to the tubing.

Several AEDs have been evaluated for their potential neuroprotective effects, including antiepileptogenicity, in both experimental and clinical studies. Temkin performed a meta-analysis of 47 studies of the effectiveness of anticonvulsant drug administration for seizure prevention and antiepileptogenicity.[46] Of these, 13 were conducted after TBI. There was no good evidence to support that anticonvulsant

drug administration after TBI is antiepileptogenic in the long term although acutely (within the first week) there was seizure reduction associated with phenytoin,[62] carbamazepine,[63] and levetiracetam.[43] Temkin emphasizes the need for "rigorous clinical trials" to determine the drug's antiepileptogenic effects as well as any neurobehavioral costs. She goes further to state that "Clinical use of any drug to prevent epileptogenesis should be avoided until clinical trials have proven the drug to be effective for that purpose" (p. 522).[46] More recently, after the completion of additional clinical trials, this same sentiment is echoed: "None of the drugs studied (phenytoin, phenobarbital, their combination, carbamazepine, valproate, or magnesium) has shown reliable evidence that they prevent, or even suppress, epileptic seizures after TBI."[64]

It is likely that there are individual differences in response to, and tolerance of, any given antiepileptic drug. Therefore, additional medications should be tried in patients who have failed to respond to or who are unable to tolerate initial treatment. In all cases, the therapeutic plan should strive for a single antiepileptic drug regimen. Monotherapy has been shown to be more efficacious than polytherapy and minimizes toxicity, drug interactions, and cost.[65] Patients who fail to respond to two or more AEDs used in appropriate doses are likely to remain resistant to pharmacotherapy. Other options, such as epilepsy surgery, should be considered in patients who are resistant to medication treatment. Surgical resections of epileptogenic zones in patients with TBI are often fraught with complications, including multifocality of epileptogenic foci, making localization difficult, as well as adhesions and scar tissue caused by previous injury or surgery.

MECHANISMS AND MODELS OF POSTTRAUMATIC EPILEPSY

When considering the appropriate treatment of posttraumatic epilepsy, it is worthwhile to understand the mechanisms whereby trauma leads to the epileptogenic state. Studies of posttraumatic epileptogenesis implicate several potential pathologic etiologies that may result in a seizure focus. These etiologies can be broadly separated into those related to the acute or primary insult (i.e., penetration of parenchyma, shearing forces, and disruption of blood–brain barrier) and those caused by late or secondary sequelae (i.e., vascular disruption, cicatricial pulling, and synaptic reorganization). Given the wide variations of brain injury and complications, it is unlikely that any single mechanism is responsible for posttraumatic epileptogenesis. Thus, posttraumatic epileptogenesis probably utilizes combinations of several mechanisms, many of which are supported by scientific studies and concur with clinical aspects of this type of epilepsy.

In 1930, Foerster and Penfield[66] induced seizure activity by electrical stimulation of areas surrounding a gunshot lesion of the cerebral cortex. These findings suggested the presence of an epileptic zone or penumbra surrounding the site of injury. Furthermore, retraction of dura that had become adherent to the damaged cortex also triggered seizures. They concluded that posttraumatic seizures are most likely to occur after dural penetration, which induces formation of scar tissue between brain and dura and subsequent pulling of the ipsilateral and, sometimes, contralateral hemispheres toward the lesion as a result of contraction brought about by normal maturation of the scar (cicatricial contraction).[66] This hypothesis is supported by clinical findings that head injuries associated with dural penetration are associated with the highest incidence of posttraumatic epilepsy (27% to 43%).[24]

Additional putative mechanisms include glial cell proliferation and damage to blood vessels, axon collaterals, and the blood–brain barrier, each of which is known to precipitate brain injury.[3,67] Jasper[67] hypothesized that the toxicity of extravasated blood increases neuronal activity abnormally in some brain regions and disrupts blood flow in others. These pathophysiologic changes could result in the alternating periods of seizure activity and functional neuronal depression that characterize acute status epilepticus induced by brain contusion.[67] Alternatively, damage to inhibitory axon collaterals by shearing forces may result in reduction of inhibitory tone and excessive depolarization that ultimately produce seizure discharges.[67] Overt penetration of dura and disruption of brain parenchyma may not be absolute requisites for posttraumatic epilepsy.

Lowenstein and colleagues reported that extradural fluid percussion induces profound decreases in hippocampal hilar neurons and hyperexcitability of dentate granule cells in rodents.[68] Postinjury hyperexcitability in the granule cell and molecular layer of the dentate gyrus has been shown to be persistent (observable at 15 weeks) and pervasive (e.g., bilateral).[69] Measures taken at earlier time points throughout the hippocampus revealed dramatic physiological and receptor-mediated disruptions in excitatory or inhibitory balance with the changes being time-dependent and only observable ipsilateral to the site of TBI.[70,71] Thus, even nonpenetrating brain injury can cause pathologic changes in distal structures, possibly tipping the balance in favor of posttraumatic seizures. These findings could help explain the emergence of posttraumatic epilepsy in persons with milder, low-velocity head injuries who do not appear to have frank penetration of dura or intracerebral bleeding.

Because penetrating brain injuries carry the greatest risk for posttraumatic epilepsy, disruption in the blood–brain barrier[72] and/or alterations in blood flow may play a role. Not only does brain injury disrupt vascularization at the site of damage, but also affected are areas "downstream" from the insult. Disruption in blood flow could bring about both ischemic and hypoxic conditions, which produce significant increases in synaptic glutamate release and decreased inactivation of glutamate. Overactivation of glutamate receptors, including NMDA receptor activation, results in excessive Ca^{++} influx,[73] which promotes phosphorylation of the $GABA_A$ receptor to its nonfunctional, desensitized state.[74] Trauma has also been associated with

GABA-mediated Ca^{++} influx,[75,76] which would not only lead to depolarization, but also potentially cell death. Loss of inhibitory neurons, coupled with other trauma-induced disruptions in normal brain function, could result in a state that both primes the brain for acute seizures and provides the foundation for long-term epileptogenic changes.

A related hypothesis implicates blood breakdown products, particularly hemosiderin, in the cellular events that lead to epileptogenesis. An important role for iron deposition has been supported by experimental studies in animals. Subpial iontophoresis of ferrous or ferric chloride into the sensorimotor cortex of cat or rat induces a chronic epileptic focus with many striking similarities to lesions in human posttraumatic epilepsy.[77,78] Electrocorticographic seizure activity is observed within 48 hours after injection, and behavioral convulsions occur between 48 hours and 5 days. These abnormalities recur spontaneously and persist for more than 12 weeks after injection.[78] Examination of the iron-induced focus reveals many histopathologic changes found in posttraumatic epileptic foci from humans[77,78]: A meningocerebral cicatrix, consisting of fibroblasts and iron-laden macrophages, surrounds the iron injection cavity with neuronal loss and gliosis occurring next to the injection site. Hypertrophied astrocytes encompass the entire iron focus. It has been hypothesized that a cascade of events is initiated by the iron focus, resulting in the genesis of a posttraumatic epileptic focus. Breakdown of blood from brain injury-induced extravasation creates iron deposits that may induce free-radical oxidant formation and subsequent lipid peroxidation.[79] In support of this hypothesis is the finding that antioxidant administration reduces the incidence of iron-induced seizure activity.[79]

The possibility of hemosiderin deposition leading to posttraumatic epilepsy has also been studied in humans.[17] Following TBI, MRI scans were utilized to detect the presence of hemosiderin, gliosis, or both. Eighty-one percent of patients showed evidence of hemosiderin deposits. Although there was no correlation between the presence of hemosiderin alone and posttraumatic epilepsy, the presence of cortical hemosiderin surrounded by a "gliotic wall" was significantly correlated with the development of posttraumatic epilepsy.

The mechanisms discussed so far largely address seizure activity that occurs acutely following brain injury. However, the onset of posttraumatic seizures is bimodal: The highest incidence occurs during the first week (early-onset seizures) with a secondary peak occurring at about 6 months.[80] This latency suggests there is a maturation process that results in the genesis of an epileptic focus. Because the latent period can last months to years after the insult in humans, much of what we know about the mechanisms underlying posttraumatic epileptogenesis comes from animal models.

The putative time course of epileptogenesis includes the following: An initial insult, such as TBI and/or status epilepticus occurs, followed by a "latent period" lasting weeks to months or even years prior to the onset of spontaneous seizures. This "latent period" represents a period during which a cascade of molecular and cellular events alters network excitability to result in spontaneous epileptiform activity. This "latent period" is also an opportunity for biomarker development and therapeutic intervention. The cascade of events that are presently suggested by experimental evidence can be classified temporally following the initial insult. Early changes occur within seconds to minutes, including induction of immediate early genes and post-translational modification of receptor and ion channel-related proteins. Within hours to days, there can be neuronal death, inflammation, and altered transcriptional regulation of genes, such as growth factors. A later phase lasting weeks to months includes morphologic alterations, such as mossy fiber sprouting, gliosis, and neurogenesis.[3,81]

Modeling posttraumatic epilepsy in animals poses quite a challenge. First, not only is it difficult to evoke spontaneous seizures secondary to TBI, chronically monitoring animals to determine when (and if) subconvulsive versus convulsive seizures occur is an enormous task. Second, because the goals of animal models vary, it may not be possible to test all aspects of interest in every model. For example, a model of posttraumatic epilepsy that attempts to mimic the postinsult latent period may not allow for neurobehavioral assessment of acute postinsult seizures or anticonvulsant drug administration. As well, such a model may not use trauma as the precipitating event. Alternatively, a model designed to assess postinjury neurobehavioral change may not allow for the assessment of the spontaneous epileptogenic process. With these limitations in mind, discussion of some of the animal models is worthwhile.

Status epilepticus, induced by excitotoxins (e.g., kainic acid or pilocarpine)[82,83] or electrical stimulation,[84–86] has been proposed to share commonalities with posttraumatic epileptogenesis.[87] The initial precipitating insult of prolonged seizures is followed by a latent period, after which spontaneous seizures occur. Like experimentally induced TBI, status epilepticus results in dramatic and significant morphological, physiological, and neurochemical alterations. Indeed, the insult-associated plasticity and neuronal reorganization seen after experimentally induced insult via seizures or frank trauma appears to share similarities.[87,88] Likewise, another useful model involves the cortical "undercut method" in which the initial brain insult is followed by a dormant period after which cortical epilepsy is evident.[89] Other models of posttraumatic epilepsy[90,91] have been developed showing spontaneous seizures following severe lateral fluid percussion injury. Seizure activity and convulsive behavior were captured via ongoing video and EEG monitoring after lateral injury. Much like human posttraumatic epilepsy, the rodent posttraumatic epilepsy model also exhibits a latent period between injury and seizure onset, and once initiated, seizure activity progressively increases over time. Indeed, this transition from TBI to posttraumatic epilepsy is a useful model in rodents[92] within which to study potential antiepileptogenic drug efficacy and other complexities related to epileptogenesis following injury.[93] Despite this promising advance, this model has not

been utilized to fully characterize the degree to which the seizure activity and postinjury drug administration impact the process of recovery from the brain injury itself. For this reason, it is worth discussing the kindling model of epileptogenesis, which has been combined with focal cortical lesion to model posttraumatic seizures and posttraumatic epilepsy and the neurobehavioral consequences of these as well as their treatment.[94,95]

The kindling model of epileptogenesis is a highly reliable phenomenon whereby a brain region can be rendered permanently epileptic when subjected to brief, repeated electrical stimulations that, alone, would not induce behavioral seizures.[96] Clinical evidence that "seizures beget seizures" is supported by a prospective study of unselected patients with new onset of seizures, and it demonstrated that the probability of seizure control was inversely related to the number of seizures experienced prior to initiation of antiepileptic drug therapy.[97,98] Furthermore, the time interval between seizures appears to decrease with subsequent episodes in untreated patients.[99]

The kindling paradigm in which the brain "learns" to seize has been used to study epileptogenesis and neuronal plasticity. Typically, electrical stimulation is administered by an implanted depth electrode and, initially, results only in a brief localized epileptiform discharge on EEG without a behavioral response. With continued daily stimulation, there are progressive increases in duration of both EEG epileptiform discharges and motor seizure activity.

The resulting convulsive behavior evolves through stages that are highly reproducible from animal to animal and may be graded by levels of behavioral severity.[100] Stage 0 is no behavioral response, stage 1 consists of chewing motion, and stage 2 consists of head nodding. At stage 3, the animal displays clonus jerking of forelimbs, and at stage 4, there is forelimb clonus with rearing onto hind limbs. The fifth and most severe stage consists of forelimb clonus with rearing and falling.

Electrical kindling of seizure activity induces neuronal changes within the brain that result in more severe generalized seizures from a stimulus that initially produced only focal seizure activity. Numerous transient and long-term changes occur during and as a result of electrical kindling with the most dramatic being seen within the excitatory and inhibitory amino acid transmitter systems.[101–106] For example, kindling significantly reduces neuronal sensitivity to GABA; the changes are long-lasting and may be seen at 4 and 12 weeks after the last fully kindled (stage 5) seizure.[107–110] Loss of sensitivity to GABA evolves during the course of kindling and correlates with seizure severity.[107] These changes are believed to result from a compensatory desensitization of the receptor in response to increased GABA release during the electrical kindling process.[111,112] Thus, the very mechanisms utilized by the brain to suppress kindling appear to be counterproductive and ultimately facilitate the kindling process.

Because sequelae of brain injury also elicit aberrations in the excitatory and inhibitory tone,[70] using the kindling model to produce postinjury epileptogenesis is a useful tool, particularly in combination with focal cortical damage. In this model,[94,95] injury severity is controlled using a reproducible focal cortical lesion[113,114] that induces behavioral deficits in animals similar to those seen in humans with brain injury.[115] This focal cortical lesion in animals does not routinely produce spontaneous convulsions, yet it does lower the seizure threshold in the amygdala. In our laboratory, we observed a 37% decrease in stage 5 seizure threshold following cortical lesion in comparison to fully kindled animals without lesions. Electrical kindling of the amygdala after focal cortical lesion is a useful and unique model as it allows for the study of the neurobehavioral impact of epileptogenesis (with and without anticonvulsant drug administration) while still controlling seizure timing, type, and number (e.g., severity).

POSTTRAUMATIC SEIZURES, EPILEPSY, AND ANTICONVULSANT PROPHYLAXIS: IMPLICATIONS FOR NEUROBEHAVIORAL RECOVERY

Brain damage resulting from TBI can significantly impair physical, cognitive, and social function. Recovery from such deficits can be variable, and ongoing disability is estimated in the United States to be present in 3 to 5 million individuals having sustained a TBI.[116] These disabilities are further compounded by posttraumatic epilepsy, which results not only in spontaneous and unpredictable seizure recurrence, but also in toxicities associated with antiepileptic drug therapies. Individuals with posttraumatic epilepsy pose a special case, in that they are neither patients with only a brain injury nor patients having only epilepsy. Thus, the treatment requirements for posttraumatic epilepsy extend well beyond those available for either the epilepsy or brain injury alone. This makes it difficult to generalize from the anticonvulsant drug toxicity and efficacy profiles obtained from epileptic subjects without brain injury, and few anticonvulsant drugs have been systematically investigated in TBI patients alone.[42,45,117–119] Treatment strategies that acknowledge these complexities will improve patient quality of life.

The controversy surrounding whether or not anticonvulsants should be administered prophylactically requires assessing the potential neurobehavioral impact of seizures versus the risk of AED administration.[117,120,121] Anticonvulsants are often administered after brain injury even though they have not been found to be effective in preventing later development of posttraumatic epilepsy.[45,46] Several early studies suggested a beneficial effect of prophylactic anticonvulsant therapy,[122,123] but later controlled studies failed to support these findings.[64] For example, when studied in a double-blind, placebo-controlled randomized manner, phenytoin administered following TBI had no impact on the later development of epilepsy although it did reduce the incidence of early seizures (i.e., those occurring within the first week after injury).[44,62]

The lack of effectiveness of anticonvulsant drugs in preventing posttraumatic epilepsy is also paralleled in experimental kindling studies. Although many antiepileptic drugs may block fully kindled convulsions in animals, they do not prevent the kindling process and do not prevent the increases in seizure severity. Specifically, phenytoin and carbamazepine may block seizures, but they do not consistently prevent epileptogenesis from occurring.[124,125] In contrast, phenobarbital and benzodiazepines do appear to be antiepileptogenic in that they are effective in slowing the progression of amygdala-kindled seizures.[126–128] Valproic acid has also been found to retard the rate of amygdala kindling but only when used at high doses with significant toxicities.[129,130] Antagonists that directly compete for the N-methyl-D-aspartate (NMDA) receptor inhibit the progression of electrically kindled seizures but have relatively less effect on seizures once kindling has been achieved.[131] This suggests a potential antiepileptogenic role of NMDA receptor antagonists that is independent of its ability to block acute seizures. A full-scale trial in which magnesium, which blocks the NMDA channel, was administered after TBI failed to show neurobehavioral benefits or antiepileptogenic effects.[64] Other transmitters have been targeted to determine their antiepileptogenicity in the kindling model as well. Administration of the alpha adrenergic receptor agonist, clonidine, can significantly retard the rate of evolution of kindled seizure stage but, by itself, does not block the fully established kindled seizure.[132,133] Thus, a key role of noradrenergic neurotransmission in the regulation of epileptogenesis has been proposed.[134,135]

The search for effective antiepileptogenic drugs may necessitate a change in current experimental drug development paradigms so that potential prophylactic drugs may be screened. Use of models of epilepsy, rather than acute seizures, holds great promise for future development of antiepileptogenic drugs. These models include the electrical kindling paradigm, studies in genetically seizure-prone animals, and models in which the focal insult (e.g., status epilepticus, cortical "undercut," fluid percussion injury) is followed by a latent period and epilepsy.[87,89–91] Ultimately, however, the effectiveness of a drug as an antiepileptogenic agent will require prospective, placebo-controlled trials in TBI and other high-risk patients with simultaneous assessment of neurobehavioral recovery.

Currently available AEDs do not appear to affect the pathophysiologic processes resulting in spontaneous seizure recurrence and may be merely masking the outward manifestations of seizure activity. The question is, does this come at a cost to the traumatically brain injured patient? The neurobehavioral effects of anticonvulsant drug therapy are known. Indeed, it has been argued that, because brain injury carries only an approximate 5% risk for posttraumatic epilepsy, the remaining 95% needlessly receive anticonvulsant medication[136] without evidence of the desired benefit: None of the drugs most rigorously tested to date display any antiepileptogenic effects, and some do not effectively suppress early seizure activity after TBI.[64] TBI patients may be unnecessarily exposed to the toxicities of anticonvulsant administration at a time when the brain is highly vulnerable to adverse drug effects. Even in normal volunteers, AEDs cause significant cognitive impairment, albeit minor in many cases.[137] Barbiturates commonly cause cognitive impairment, even at low doses.[138] For many drugs, however, toxic levels can account for some of their untoward effects. For example, it was initially suggested that carbamazepine induced less cognitive impairment than phenytoin.[139] When the data were reexamined so that patients with toxic phenytoin levels were removed from the study, no significant differences in cognitive impairment could be found between treatments.[140] A subsequent study, which maintained levels in therapeutic ranges, verified these findings.[138] Although valproic acid is thought to cause minimal problems with cognition, withdrawal of this medication improved psychometric scores.[141] In a study that included completely randomized assignment of drug versus placebo, phenytoin administration after TBI was associated with impaired function on several neuropsychological measures of cognition, which are among the most common and disabling problems faced by individuals with brain injury.[117] Phenytoin and carbamazepine have each been shown to adversely affect psychomotor function following brain injury although this is reversible upon drug discontinuation.[119] The newer AEDs have not been studied for their effects on cognitive function in patients with TBI although, in individuals with epilepsy, many of these drugs exhibit a better neuropsychological profile than the older drugs[54,142] These negative consequences of treatment with AEDs on cognitive functioning are not surprising when one considers anticonvulsant drugs can adversely affect cognitive function in non-brain injured individuals[137,143,144] and that drug sensitivity is greater after brain injury. To address these issues, it has been recommended that anticonvulsant prophylaxis be utilized in high-risk patients (e.g., those with severe TBI) and only for the first week after injury.[45,145]

Animal studies addressing these issues paint a similarly negative picture. For example, if diazepam is administered during the first 3 weeks after unilateral anteromedial cortex damage, recovery from somatosensory deficits is delayed indefinitely.[114] Even if diazepam is administered only for the first 7 days after brain damage, recovery is significantly delayed.[146,147] Phenobarbital also appears to interfere with somatosensory and motor recovery following brain damage in rats and nonhuman primates[148,149] as does phenytoin.[150] Not all anticonvulsant drugs have been found to be detrimental after brain damage in animals: Carbamazepine[151] and vigabatrin[152] had no impact on recovery from somatosensory deficits. As a caveat, however, when an anticonvulsant dose of vigabatrin was coadministered against subconvulsive kindled seizures, recovery was impeded.[153] Similarly detrimental to functional recovery was phenobarbital administration prior to evoked subconvulsive seizures.[154] These data suggest that the interaction between anticonvulsant drugs and subclinical seizures after brain insult are detrimental to functional recovery, and the net

effect is greater than either factor alone. There may be some value in EEG monitoring after TBI,[17,30] not only as a means of detecting subclinical seizures, but also to influence treatment strategies that optimize neurobehavioral outcome.

There are several potential mechanisms by which anticonvulsants may adversely affect the recovering brain. First, these drugs suppress repetitive firing, which is important for long-term potentiation (LTP), a phenomenon associated with learning. LTP is discussed in the chapter by Lehr in this volume. Second, barbiturates and benzodiazepines directly modulate the $GABA_A$ receptor and increase neuronal inhibition. That there is a link between enhanced postsynaptic GABA-mediated inhibition and impaired functional recovery is well established.[114,146–149,155–157] Likely mechanisms include toxicity of excessive intracellular Cl^-[158,159] and Ca^{++}[75,76] associated with GABA postinjury, GABA receptor-dependent excitotoxicity,[160] and decreases in growth factor production attributed to GABA augmentation.[161] Finally, suppression of repetitive firing or general CNS depression could be counterproductive following brain injury, especially because neuronal depression already occurs as a consequence of brain injury. This condition of postinjury neuronal depression has been referred to as diaschisis,[162] which is the temporary disruption of neuronal activity in undamaged areas functionally related to injured areas.

Evidence that diaschisis occurs after brain injury has been well established with measures of blood flow, metabolism, electrical activity, and neurotransmitter levels.[163–166] Moreover, this depression of neuronal activity after brain injury has been correlated with behavioral deficits, and restoration of normal neuronal activity correlates with behavioral recovery.[167–169] The use of positron emission tomography (PET) has made it possible to measure posttraumatic neural depression after brain injury in humans. Measures of cerebral glucose metabolism clearly show a state of metabolic depression postinjury, and the relationship between this and functional level depends on outcome measures utilized although persistent metabolic disturbances post-TBI, especially within critical periods, have been linked to poorer outcome.[170] In general, the level of posttraumatic neural depression is commensurate with the precipitating insult and correlates with outcome: The more severe the insult, the greater the posttraumatic neural depression, and the greater the posttraumatic neural depression, the greater the behavioral deficit.[171]

Based on the brain's functionally depressed state after trauma, it has been hypothesized that posttraumatic seizures may be the result of adaptive mechanisms initiated by the injured brain in its attempt to restore normal neuronal activity. For this to be the case, the neurobehavioral consequences of seizures would need to be associated with improved recovery or no deleterious effect (e.g., neutral). Experimental data in animal studies suggest the effects of seizures are not uniform and greatly depend on seizure type, severity, and frequency. For example, mild or infrequent seizures have been found to improve the recovery.[172–174]

At first blush, these data may seem counterintuitive. However, when the entire array of neural and functional consequences of seizures are considered, a complex yet fairly clear picture emerges that is dependent on the timing, type, and severity of postinjury seizures. For example, using an animal model of posttraumatic epilepsy (described above), it appears that the impact of seizures is bimodal: Convulsive seizures (stage 1) during the 6-day postlesion critical period are detrimental to the recovery process whereas subconvulsive seizures (stage 0) have no functional impact.[94,175] This effect is time-dependent and hemisphere-specific in that stage 1 kindled seizures occurring on postlesion day 7 or later have no impact on the recovery process. Moreover, contralaterally kindled seizures exert no impact on recovery regardless of when they occur. We propose that the occurrence of early stage 0 kindled seizures after cortical lesion models early posttraumatic seizures, and the occurrence of early stage 1 kindled seizures after lesion models posttraumatic epilepsy. As such, our results suggest that the occurrence of early posttraumatic seizures does not adversely affect recovery from the brain injury, but early posttraumatic epilepsy blocks recovery completely. Potential mechanisms for the behavioral effects of early posttraumatic seizures (stage 0) versus early posttraumatic epilepsy (stage 1) include fibroblast growth factor-2 (FGF-2). Specifically, stage 0 seizures exert no impact on the time course of peak FGF-2 expression whereas stage 1 seizures block this important neurotrophic contributor to functional recovery.[176] Moreover, early posttraumatic seizures followed by the later development of posttraumatic epilepsy had no impact on functional recovery and no impact on FGF-2 expression. In contrast, even a single epileptic seizure (stage 1) within the 6-day postlesion critical period in our model blocked recovery for the duration of testing in addition to blocking FGF-2 expression. Interestingly, kindled seizures in nonbrain injured animals have been associated with neurogenesis,[177,178] which may contribute in a positive or negative way to the recovery process, depending upon whether these new cells replace lost ones, make functionally relevant connections, or contribute to aberrant plasticity (e.g., excitability that might contribute to epileptogenesis).

There is other evidence that seizure effects vary. Clinical studies have shown that simple abnormal EEG activity is associated with impaired cognition[179] and that response time is impaired even during single focal interictal spikes in humans.[180] Learning is also impaired in young rodents undergoing repetitive and frequent audiogenic seizures.[131] In contrast, repetitive kindled seizures do not appear to affect most aspects of learning[181,182] although some components of learning (e.g., acquisition) are impacted by the transition from partial to generalized seizures.[181] There are some data suggesting that the seizure activity and convulsive behavior, in and of itself, may not be responsible for adverse cognitive effects. Instead, opioid receptor activation may be responsible: pentylenetetrazol (PTZ) kindled animals failed to exhibit impairments on the Morris water maze when the opioid antagonist naloxone was administered prior to PTZ

kindling[183] even though both groups of PTZ-kindled animals exhibited the same degree of seizure activity. Taken together, these data suggest that although, in some situations, seizures may inhibit learning, the seizure activity, in and of itself, may not be sufficient to impair learning. Instead, it is the underlying physiological processes (e.g., opioid activation) that seizures trigger that leads to deficits. Finally, brief seizures do not necessarily cause brain damage,[106] yet prolonged seizures cause neuronal death via excitotoxicity.[87] This latter type of seizure activity following trauma would likely contribute to further cell death or interfere with the plasticity underlying recovery processes.

Seizure number and timing may also contribute to outcome clinically. Using deidentified data from the University of Washington TBI Data Repository, we (TDH and KTL) assessed the relationship between neurobehavioral outcome and seizure activity after TBI, both short and long term. Of particular interest was the impact of seizure number and timing on functional outcome following TBI. Data on neurobehavioral outcome from two prospective studies were retrospectively reviewed. In the first study, patients were randomly assigned to receive either prophylactic phenytoin or placebo following TBI in a double-blind study design.[62,117] Prophylactic medication was administered for 1 year, and patients were observed for an additional year after medication was discontinued. In the second study, patients were randomly assigned to receive either valproate or phenytoin prophylactically following TBI.[118,184] Patients were randomized to one of the following three conditions: valproate for 1 month followed by placebo for 5 months, valproate for 6 months, or phenytoin for 1 week followed by placebo for the remainder of 6 months postinjury. Neurobehavioral outcome in both studies at 1 month and 12 months postinjury were analyzed. In the two prospective trials, it was found that phenytoin, in the more severely injured patients, was associated with poorer neurobehavioral function at 1 month, but not 12 months post-TBI, and valproate had a "benign" neuropsychological profile following TBI.[117,118] Using the same data, we performed an analysis of seizure number and timing with an additional analysis of other, non-study-related drugs (benzodiazepines and nonbenzodiazepine anticonvulsants). Early seizure activity (within 1 week postinjury) in the phenytoin study had no significant effect on neurobehavioral recovery on any of the outcome measures at 1 month postinjury. In the valproate study, however, seizure activity in the first week predicted poorer 1-month outcome on a neuropsychological test composite score, Glasgow Outcome Score (GOS), and number of new or worse symptoms reported. The number of early seizures was found to affect outcome with three or more seizures in the first week post-TBI associated with worse outcome compared to one to two or no seizures. Benzodiazepine coadministration did not contribute to this finding. In both studies, however, seizures in the first week were not predictive of neurobehavioral outcome at 12 months postinjury. Furthermore, late seizures (after the first week but within the first month postinjury) did not affect neurobehavioral outcome assessed at 1 or 12 months postinjury in either study. Timing of and number of seizures play a significant role in the impact of seizures in clinical populations, much like that seen in animal studies. That the basic and clinical data are corroborative is important when considering when and if to treat seizures in humans after TBI and prior to a diagnosis of epilepsy. Understanding the critical role of seizure timing, type, and severity has important implications for optimizing functional outcome after TBI.

Although seizures, per se, may not be detrimental to functional outcome, there is significant evidence suggesting that posttraumatic epilepsy poses significant problems for rehabilitation of the TBI patient.[185] The uncertainty caused by randomly occurring loss of consciousness places yet an additional barrier to independence. At worst, uncontrolled epilepsy may necessitate placement in specialized care facilities and, at the least, may prohibit driving privileges. Uncontrolled seizures are also associated with a significant risk of trauma and unexpected death ("SUDEP").[186] Some data suggest the impact of posttraumatic epilepsy on neurorehabilitation may extend beyond these social aspects and could actually impede brain recovery. World War II veterans with head injury who developed posttraumatic epilepsy had a lower survival rate than veterans without epilepsy.[187] The incidence and severity of cognitive deficit in hemiplegic children is highly correlated with the presence of seizure activity, independent of the amount of cerebral damage.[188] A retrospective study of head-injured patients demonstrated that functional measures were lower in patients who developed posttraumatic epilepsy upon entry into rehabilitation than those who did not. Although both groups improved significantly, functional outcome remained lower in the epileptic group.[189] Importantly, these studies could not address the question of whether the results were due to seizures, injury severity, or anticonvulsant drug administration. Haltiner and colleagues[190] were able to tease apart some of these issues: When injury severity is controlled, neither late posttraumatic seizures nor posttraumatic epilepsy had an influence on neuropsychological outcome measures.

To effectively delineate the neurobehavioral impact of seizures versus epilepsy following TBI in humans, it is necessary to know when and if the patient is having seizures. Assessing seizure timing, in the analysis of phenytoin and valproate study data from the University of Washington TBI Data Repository discussed above,[62,117,118,184] we found seizure activity within the first week postinjury in the valproate study to predict poorer neurobehavioral outcome at 1 month postinjury, with three or more early seizures associated with worse outcome compared to one to two or no seizures. However, in both studies, neither early seizures (within the first week post-TBI) nor late seizures (after the first week but within the first month post-TBI) were predictive of neurobehavioral outcome at 12 months. In another study investigating effects of seizure timing on outcome, Vespa and colleagues[30] continuously monitored patients after TBI for up to 14 days. Twenty-two percent of these individuals had clinically evident or nonclinically

evident seizures. When comparing outcome between these individuals and those in the nonseizure group, it appears that seizures are not necessarily detrimental. For example, both groups exhibited increased intracranial pressure (ICP) after brain injury, but the overall ICP was actually greatest in the nonseizure group. Cerebral perfusion pressure (CPP) was slightly, although significantly, lower in the nonseizure group. There was no difference between the groups in terms of length of stay, nor in outcome (GOS): Both good and poor outcomes were equally likely regardless of whether there had been seizures. Even though there was a greater mortality rate within the seizure group, this could be fully accounted for by those individuals with status epilepticus. If these individuals were removed from the analysis, it appeared that the seizure group had a lower mortality rate than the nonseizure group. It is also worth noting that Vespa and colleagues[191] have shown that postinjury seizures can be correlated with elevated glutamate levels as assessed by intracerebral microdialysis. Elevated glycerol, a marker of membrane damage, was reported in one patient with posttraumatic status and in another with posttraumatic electrographic events without status.[192] It remains unclear whether these results are only specific to instances of postinjury status epilepticus or generalizable to other types of recurrent seizure events. Moreover, what any of these findings mean for functional outcome has yet to be determined.

In summary, experimental data suggest the effect of seizures on functional recovery of the injured brain is not uniform and depends on seizure timing, type, and severity. Specifically, recurrent and/or severe seizures may have a negative impact on recovery, and mild, infrequent seizures may be associated with improved behavioral recovery or be without neurobehavioral consequence. Results from our analysis of the University of Washington TBI Data Repository phenytoin and valproate studies suggest that seizure activity and, specifically, the number of postinjury seizures in the first week after TBI relate to outcome in the short term but not in the long term. Specifically, data from the valproate study suggest that three or more seizures in the first week after TBI are associated with poorer neurobehavioral outcome at 1 month but not 12 months. This supports that seizure timing, type, and severity each contribute to the short- and long-term impact of seizures on functional outcome. Moreover, there appears to be a combination (timing/type/severity) of seizure activity that is not associated with adverse consequences as well as another combination with which seizures are sufficiently severe to cause further brain damage or frequent enough to develop into epilepsy, potentially interfering with behavioral recovery and quality of life.

CONCLUSIONS

The accurate diagnosis of episodic behaviors is crucial to providing the most appropriate therapy for TBI patients. Although posttraumatic epilepsy is a common entity, it may be difficult to recognize. Posttraumatic epilepsy must be carefully distinguished from other types of behavioral spells because either unnecessary AED therapy or uncontrolled seizures may potentially impair neurologic recovery. At present, there is little evidence to support long-term prophylactic use of anticonvulsants in TBI patients. Their use in this way does not prevent epileptogenesis clinically, and much data implicates negative effects on cognition and recovery of brain function. Thus, AED therapy should be withheld until there is a bona fide diagnosis of epilepsy. Once the diagnosis of epilepsy is secure, effective therapy should be initiated promptly to prevent the deleterious effects of uncontrolled seizures on brain recovery. Future research will need to address whether control of posttraumatic epilepsy improves functional outcome and if these gains outweigh the adverse effects of AED therapy. In addition, the mechanisms of posttraumatic seizures will need to be better understood so that therapies that prevent epileptogenesis may be achieved.

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PART 3

Therapy

22

Evaluation of traumatic brain injury following acute rehabilitation

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INTRODUCTION

The field of traumatic brain injury (TBI) rehabilitation has changed considerably over the last 45 years. The field was born in the late 1970s of a need realized largely by the private insurance community in the United States. People with TBI were living far longer than ever before, and rehabilitation efforts for these individuals were not well developed.

In the early 1980s, a number of hospital- and nonhospital-based rehabilitation programs developed utilizing a variety of program models and concepts. The number of facilities available to people with TBI increased dramatically in the mid-1980s, only to contract again in the early 1990s with the advent of managed care. Early rehabilitation efforts were largely developed using treatment techniques developed for other populations and applied to the TBI population. The last 45 years have seen a great deal of refinement of interventions and improved predictability of outcome.

The impact of managed care on TBI rehabilitation has been considerable[1,2] as it has been in many areas of medicine. Perhaps the largest single impact, however, can be seen in the amount of treatment provided to people with TBI. The 1980s saw a broadening of insurance coverage for rehabilitation for people with TBI, but as managed care took hold, significant decreases in length of stay (LOS) were noted. The average LOS for acute hospitalization decreased from 29 days in 1990 to 19 days in 1999. LOS for acute rehabilitation hospitalization decreased from 48 days to 28 days from 1990 to 1999. It is clear that severity of injury did not change during this time.[3] Kreutzer et al.[2] reported decreases in LOS averaging 3.65 days or 8% annually for acute and inpatient rehabilitation treatment of TBI between 1990 and 1996. We now see LOS for acute rehabilitation hospitalization averaging in a range of 10 to 14 days, depending upon location. Inpatient rehabilitation hospital stays now may be moderated by pressure to discharge patients earlier, either to a skilled nursing facility (SNF) or home setting.

It can be argued that alternative treatment settings allow LOS to be decreased as noted above for these periods, and it is likely that such availability does, in fact, contribute to shorter LOS. The point, however, is that these individuals are discharged from acute care settings far earlier than has ever been accomplished before. Consequently, alternative care settings are increasingly faced with individuals who are admitted with ongoing medical needs or with, perhaps, as yet unrecognized problems. The trend toward shorter LOS has sharpened and provides a substantial challenge to the families and professionals involved with this population. The evaluation of a person with TBI becomes far more complicated than ever before as a result.

TBI, unlike any other diagnosis, can impact an exceptionally broad spectrum of systems. Additionally, recovery from TBI can occur over a protracted course of time[4–11]

with residual deficits observable for many individuals on a lifetime basis. TBI will impact the injured person and his or her immediate family for life for persons who sustain moderate-to-severe injury.[12–17] Data suggest that even a small percentage of people who sustain mild TBI (MTBI) will experience symptoms that persist for months or years postinjury.[18,19]

Evaluation of a person with TBI, then, truly requires a great deal of investigation, time, and thoroughness. Unfortunately, many forces conspire to thwart the completion of such evaluative efforts. Discharge planners have relatively little notice of impending discharge requirements. They are plagued with lack of financial coverage for ongoing rehabilitation or placement in supervised settings for many individuals. Discharge planners understand that families are ill equipped to provide all the necessary care for an injured family member but often have no choice in such placements. The discharge planner may be unaware of resource availability due to the busy nature of his or her caseload and a resultant inability to carefully research discharge options that may exist locally, regionally, or nationally. Finally, allied health employee turnover in these positions contributes to the lack of familiarity with available resources.

Discharge planners can be proactive when working with an acute inpatient brain injury rehabilitation unit. Identification of potential discharge options for continued rehabilitation treatment at the time of admission or very nearly after admission allows postacute treatment facilities maximum time to check benefits and negotiate payer acceptance of admission to a postacute treatment setting. This allows the acute treatment team the broadest array of discharge options to be developed and with far less time pressure. Early referral does not have to constitute a commitment to transfer a patient to any particular follow-on setting. Early referral does not necessarily imply that the patient will require additional evaluation or treatment at the time of discharge—only that benefits can be checked and negotiations started should ongoing care be necessary. Postacute rehabilitation facilities have developed relationships and means of explaining their work to payers, and the professionals in these settings are skilled at facilitating access to ongoing treatment. This can ease the burden of determining a discharge disposition for the discharge planner considerably. The discharge planner should maintain a resource center of discharge options along with materials that describe those options to the rehabilitation team, patient, and family. The discharge planner can also ensure that the medical record is readily accessible to the evaluator along with appropriate consents completed. The record should contain a recommendation from one or more physicians involved in the patient's care, depicting the need for ongoing postacute rehabilitation for the payer's benefit.

The evaluation of a person with TBI is frequently required on short notice and must be conducted in a busy, if not harried, environment in which insufficient time disallows for complete collection and collation of necessary information for the evaluator. The evaluation today must be conducted far more quickly without sacrificing thoroughness or accuracy. More than ever, discharge planners and others need to rapidly know the results of the evaluation, whether an individual is acceptable for admission to the next level of rehabilitation, and whether the individual can be admitted to that next level. The evaluation, then, must be conducted quickly and thoroughly, a report of the findings generated, and all parties informed of the findings and available ongoing treatment options—often in the span of 24 to 48 hours. The evaluator must be supported by a team of professionals who can rapidly react to the demands of today's rehabilitation and funding milieu. Of course, some evaluations may be conducted in a home, SNF, jail, or psychiatric hospital. In many of these situations, there is far less time pressure to complete the evaluation and greater difficulty in collecting relevant medical records.

This chapter outlines the comprehensive nature of information that should be collected during an evaluation. It should be recognized that complete collection of the information to follow is unlikely in today's medical rehabilitation and funding environment; however, information that is not collected should be earmarked for later collection should the evaluation recommend progression to a next level of rehabilitative intervention or admission to another care setting. It should also be understood that the intention of this chapter is to provide information to the facility-based evaluator who must conduct evaluations at the bedside, in the home, or in another institution. Thus, the evaluation outlined is not designed to be exhaustive, but rather to identify the major issues at hand. Many of these issues will require much more extensive work-up than is intended to be represented here after admission to a "next level" of care.

PREPARATION

> So much of our time is preparation, so much is routine,
> and so much retrospect, that the pith of each man's genius
> contracts itself to a very few hours.
>
> *Ralph Waldo Emerson*

Evaluations proceed best when the evaluator has the opportunity to prepare in advance of the evaluation. Demographic information, such as name, age, date of birth, date of injury, social security number, home address, telephone numbers, insurance carrier information, and so on, should be recorded for easy reference during the evaluation. Precious time will not be taken up by these activities in this manner. Although race is generally documented, ethnicity is less often noted. Recent detailed recommendations suggest recording both.[20] The evaluator should be very familiar with the complexity of TBI and with the scope of service availability on a local, regional, and national level. All too often, evaluations are conducted to determine whether an

individual is appropriate for admission to a specific rehabilitation or assisted-living setting. This does not pose a significant problem when the individual is appropriate for admission; however, the evaluator has an ethical responsibility to recognize when an individual may be better served in an alternate environment. In order to accomplish this, the evaluator should be aware of services offered at a variety of settings other than that in which he or she is employed. Careful consideration must be given to advice offered for the types of treatments or care that should be delivered next for an individual as well as to where those services might be available. Occasionally, evaluations are conducted for the sole purpose of securing an admission to a facility, in which case the evaluator has breeched ethical principles.[21]

The evaluation is best served by review of medical records prior to seeing the individual. Collection of medical records can be quite challenging. Medical records are available from treatment centers; however, access to the records can be quite difficult. Medical records departments are charged with maintenance of confidentiality and are frequently overwhelmed in their workload. Although some states have requirements for timed compliance with requests for medical records, obtaining records via mailed or even hand-delivered requests can be exceptionally arduous. Thus, discharge planners, referring physicians, or other professionals can facilitate access to records for an evaluator. The advent of electronic medical records has substantially reduced the burden of transmitting medical records to subsequent treaters.

Medical records may be more readily available in the files of workers' compensation carriers and, sometimes, accident and health carriers because these companies strive to pay only those bills that are accompanied by medical records. The availability of such records can be useful in cases in which the individual being evaluated was injured not recently, but sometime in the past. It will not always be possible to review the entire medical record prior to completion of the evaluation. The evaluator's role, then, is to note which records have been reviewed and to begin the process of obtaining the balance of the unreviewed records for immediate review and consideration upon receipt. Incomplete record availability should be noted in the evaluation report, and the report should be amended should newly received information materially change any information or recommendations in the report.

Evaluation of a person with an acquired brain injury presents an opportunity to systematically gather and record information for the individual's benefit, of course. It also provides an opportunity for the professional community to utilize a standardized approach to information collection so that research and outcome data can be better compared across treatment settings. To that end, the National Institute for Neurological Disorders and Stroke (NINDS) undertook development of a Common Data Elements (CDEs) project in 2009.[20,22] These efforts provide a starting point for development of a more thoughtful and systematic approach to understanding this complex population.

The developers of the CDEs point out that assessment of individuals with TBI may occur immediately after onset of injury or may occur later. In the latter instance, assessment may constitute both the end of one phase of treatment, i.e., acute care, as well as the beginning of another phase of treatment, e.g., postacute rehabilitation. To that end, the degree to which evaluation can follow an internationally sanctioned approach to information collection and documentation will necessarily impact the ability to conduct cross-platform research.

The CDEs are currently primarily focused on acute medical treatment. They address eight main categories, most of which are germane to all levels of treatment. They include 1) participant/subject characteristics, 2) participant and family history, 3) injury-/disease-related events, 4) assessments and examinations, 5) treatments/interventions, 6) protocol experience, 7) adverse events and safety data, and 8) outcome and function. Each category has substantial detail, and great emphasis is placed on use of standardized reporting formats to enable consistent data collection. These formats are available for review and incorporation into clinical and research electronic data collection formats.

Review of the medical record should begin with records created at the time of injury. The accident scene detail should be reviewed to attempt to determine the detailed nature of the injury that includes the place and cause of injury, likely levels of force encountered by the body, numbers of blows to the head, details pertaining to level of observed consciousness or alteration of consciousness, emergency procedures completed prior to emergency room arrival, length of elapsed time to emergency medical treatment, reported observations of patient status by witnesses and emergency personnel, and Glasgow Coma Scale (GCS) score observed at the scene.[23] The GCS is used to both assess the severity of injury and track the course of recovery. Mild brain injury is defined by a GCS score of 13 to 15. A rating of 9 to 12 is classified as a moderate injury, and a rating of 3 to 8 as a severe injury. In instances in which the GCS is used to document the course of recovery, notation of medications being administered over the interval should be made as medications can materially impact ratings of depth of coma.[24] The Abbreviated Injury Scale[25] is now recommended for assessment and documentation of the severity of extracranial injuries.[20] Calculation of the injury severity score is also recommended at the acute level of treatment.[26]

Blood alcohol levels can also confound GCS scores and should be noted. Emergency room records may reveal information as indicated above and will begin documentation of the observed injuries upon presentation to the emergency department. Recent recommendations suggest use of four categories in description of injury type: closed, penetrating, blast, and crush.[20] Increasingly, details such as level of consciousness and trauma scores are being placed and monitored in the charts as emergency departments become more sophisticated in their approach to TBI intervention. These data points are important to collect as they bear upon most outcome predictions available in the literature. The CDEs

recommend documentation of GCS, duration of posttraumatic amnesia (PTA), duration of loss of consciousness (LOC), and duration of alteration of consciousness (AOC) as basic neurologic assessments.[20] Further, information for prognostic modeling developed from the IMPACT[27] and CRASH[28] prognostic studies is recommended for inclusion in basic acute medical data sets and may be gatherable at or near the time of evaluation.

As the medical record progresses, it is tempting to confine one's review to the more easily read typewritten reports. Clearly, these records provide a fairly comprehensive review of a case; however, important details may be found in the handwritten nursing, therapy, and physician notes. As the evaluator reviews the case, questions will arise as to how and when developments occurred, or conflicting information may be found in different portions of the medical record. The answers to such questions can often be found in handwritten notes. The record is best understood when reviewed and presented in the evaluation report in chronological order.

Care should be given to noting admission and discharge dates, especially in the case of multiple-facility involvement. All conditions diagnosed must be included in the report together with a detailed review of medications, their effects, and reasons for use and discontinuation. The evaluator is well advised to structure the collection of information so as to increase the likelihood that the most thorough evaluation will be completed. To that end, Appendix 22-A provides such an evaluative format that is useful in structuring the evaluation process and in report preparation. Information that is not collected is obvious by its absence on this form and, as the evaluator considers finishing the evaluation and whether enough information has been gathered, the form provides a means for such assessment.

The evaluator should approach each evaluation in as uniform a manner as possible. Certain of the sections to be reviewed in this chapter require use of some minimal equipment and familiarity with certain procedures. Standardized reporting of level of disability is strongly suggested by accreditation agencies[29] and should begin at the time of the evaluation. The evaluator will need access to all rating scale forms utilized by the organization with the heading information already completed. This will speed completion of the rating scales, increasing the likelihood that they are completed. Scales most often used are the GCS, the Rancho Los Amigos Scale,[30] the Disability Rating Scale,[31] and the Functional Independence Measurement Scale.[32] The reader is reminded to consider adherence to the NINDS CDEs data collection advisories for potential other scale usage.

The evaluation is conducted for the purpose of determining the history and current status of the individual with an eye toward determination of the need or propriety of additional treatment or placement. The evaluator should have a thorough working knowledge of various treatment approaches and techniques available so as to be in the best position to make recommendations about ongoing treatment delivery. Although the focus is largely upon the injured individual, the evaluator has a role to play in education of the individual's family and friends as well as the professionals currently involved with the person. As such, evaluations will require an investment of energy and time unlike that seen in many other diagnostic groups. Evaluations of people with TBI can require well over 2 to 4 hours and still remain incomplete. There is a huge amount of information necessary to collect that will shape the rehabilitative effort and the current and future discharge planning. Information collected during the evaluation will set the stage for the more in-depth clinical assessments to be conducted once an individual is admitted to the next level of care being considered. Although it may be tempting to put off collection of some information until after the admission, the propriety of that very admission may be impacted by advanced knowledge of key variables. Prognostication of outcome is often requested at the time of evaluation, and the accuracy of such prognostication can only be detrimentally affected by a lack of comprehensive information.

The evaluation should begin with answers to the questions below:

- What is the purpose of the evaluation?
- Who requested the evaluation to be completed?
- What is expected following the evaluation and by whom?
- Who are the various people who are to be involved in the evaluation?
- What specific questions have been posed to be answered by the evaluation?

The evaluation's purpose may be to determine whether an individual is ready for admission to a next level of care or treatment, or it may be conducted for medical–legal purposes. Insight into the purpose of the evaluation is often, although not always, provided by the person who requests the evaluation. The purpose may or may not be well articulated. The evaluation may be conducted at the request of a person behind the scenes with or without the encouragement of the people currently involved in the individual's care. Consequently, some diplomacy may be in order. It is quite important to understand what is expected as an outcome of the evaluation. Because there is so much information that can be collected in an evaluation, the amount of time to complete the evaluation will be dependent upon what those expectations are. The evaluator should be very clear as to what information he or she may be expected to provide, what opinions he or she may be asked to provide, and the information he or she will have to obtain in order to adequately answer those questions. The people involved can be quite variable from case to case.

Likewise, roles played by these parties may not be obvious. It should not be assumed that a person's spouse is the primary decision maker, for example. Some spouses defer to parents, siblings, friends, or others. Thus, the evaluator must determine who the key players are and their roles to ensure that communication flows smoothly before, during,

and after the evaluation. It is usually advisable to have the major players present and/or available during the evaluation. The evaluator can use their presence as an opportunity to educate regarding the findings of the evaluation, either as the evaluation unfolds or in summary at the end of the evaluation. Caregivers, understandably, have information as their most intense need and desire.[33,34]

The evaluation can be conducted using a variety of formats in combination with one another. Direct interview and assessment of the injured person may or may not be possible as a means of information collection. It may be necessary to glean information from observation of the injured person as he or she interacts with other allied health professionals or with family and friends. It will be important to be able to interview these parties as well to obtain information that is unlikely to be well represented in the existing medical record. This includes information concerning preinjury matters, such as educational achievement, vocational history, social and family history, and, sometimes, medical history. In the event that information is relied upon from medical records to substantiate a particular matter, care should be taken to note the currency of the report because recovery in TBI sometimes occurs at unpredictable rates.

EVALUATION

Current medical status

The person's current medical status is a primary focus of the evaluation, especially in these days of shortened hospital LOS. Current medical status cannot be truly understood, however, without reference to medical history, both prior to and since injury. Every effort should be made to thoroughly review medical history information. Laboratory studies should be reviewed for reported abnormalities with particular attention paid to neuroendocrine function,[35,36] blood dyscrasia, serum anticonvulsant levels, prothrombin times, infectious disease reports, and alkaline phosphatase levels. Current medical status reporting should include a detailed review of bowel and bladder status and continence. This should include catheter requirements, stool softeners, levels of independence and awareness, and any medical issues noted. Dietary status should review nutritional intake, swallowing status, and level of independence. A good depiction of the history of swallowing evaluations is in order in the event that the person suffers from dysphagia.

A full description of medications, dosages, and indications should be provided. Medication history since injury should be reviewed and reported chronologically, together with indications, effects, and reasons for discontinuance. Additionally, matters impacting compliance with medical recommendation by the patient or family is strongly suggested. This includes the individual's or family's perspectives on use of prescription and nonprescription medications, supplements, recreational drugs/substances, nutritional approaches, and religious convictions that manifest during treatment. These matters can materially impact prognostication. Seizure history, or its absence, should be noted. All allergies must be clearly documented. The individual's most current height and weight statistics, together with behavioral health concerns, such as alcohol or substance abuse, must be reported.

Dental status should be reviewed, either via the records or via examination.[37] Broken or missing teeth will need to be addressed. The reliance upon dentures, orthotics, or dental appliances should be noted. The oral cavity should be examined for description of the dentition and gums. Some anticonvulsants and other medications can cause gum hyperplasia.[38] Oral hygiene and level of independence and efficiency should be reported. Oral tactile defensiveness may be a clue to painful teeth or gum. Inspection of the buccal cavities for food residue may suggest lingual motility or swallowing problems.

It is important to review the person's sleep as sleep disorders following TBI appear to occur related to the TBI.[39,40] Check for sleep routine, including bedtime, arise time, nighttime awakening, reasons for awakening, and how the person feels upon awaking in the morning. Note caffeine or other stimulant intake as well as medications or substances used to induce or maintain sleep. Note any sleep studies that have been conducted, devices used during sleep, and sleep medications that have been prescribed in the past or currently. Discussions of sleep can be found in Chapters 11 and 31.

The person's preinjury medical and behavioral status should be documented.[20] This should include the person's personal history as well as family history that might become contributory to developing health concerns in the future or outcome prognostication. This should include both physical and emotional health issues. This is particularly important for individuals of advanced age who are more likely to have comorbid conditions at the time of injury, for children or adolescents who may be medicated, or for those who may have engaged in substance abuse either as a person using or selling legal or illicit substances. Careful investigation should be conducted into the history of previous trauma to the head or whiplash as this information may be instrumental in understanding the postinjury course of recovery, particularly in the case of MTBI.[41] The CDE recommendation is for documentation of lifetime history of TBI via the Ohio State University TBI Identification Method short form.[42]

Last, medical interventions that may be necessary in the future should be recorded, such as revisions of orthopedic appliances, gastrostomy or tracheostomy sites, cranioplasty, and so on. Such procedures may be best undertaken either prior to or during additional rehabilitation depending upon the nature of the case. Additionally, knowledge that more than one surgical procedure will be necessary in the future may allow for scheduling of both procedures under a single anesthesia.

Audiometry

Audiometric evaluation is not generally performed in the early phases of rehabilitation for TBI. Where formal

audiometry has been undertaken, the dates of testing and detailed findings should be reported. In instances in which formal testing has not been undertaken, observation of the individual's functioning within the environment can provide valuable insight into audiometric function. Historical information is of great importance to be gathered during this process. It is important to know whether there was a blow to the head, the integrity of the tympanic membranes, and whether otorrhea was reported.[43,44] Each of these is important for the possible identification of disarticulation of the ossicular chain within the middle ear. It is not always possible to view tympanic membrane ruptures or tears. To that end, some individuals will produce sounds emitting from the external auditory meatus when conducting a Valsalva maneuver. This is indicative of a tear in the membrane.

Temporal bone fractures may result in cochlear or vestibular damage.[43,44] A blow to the head in the temporal region may impair cranial nerve VII function by damaging the nerve as it exits the skull, possibly impacting either lacrimation alone or lacrimation and salivation.[45,46]

Additionally, historical information, such as exposure to noise of a chronic nature in the pursuit of recreational or vocational interests, might portend the development of sensory neural hearing loss. Of course, sensory neural hearing loss of this type does not arise from the TBI but may complicate communicative and other restorative efforts. Likewise, an individual's chronic exposure to ototoxic medications, such as certain antibiotics and aspirin, might lead to loss of hearing. Reports of tinnitus are common and may be described in varying terms. Terms used by the person to describe tinnitus can be important in understanding its underlying cause. A high-pitched whistling or buzzing sound is most often experienced. The tone is most noticeable in quiet areas and is masked by normal environmental noise levels. Some tinnitus, however, is reported as a roaring and may suggest significant otological pathology, such as posttraumatic Ménière's. The evaluator must note these issues as well as whether the tinnitus is constant or variable.

Behavioral observation and interview may assist in identification of hearing loss. The evaluator should note whether the individual with lesser communicative abilities attempts to read lips or localize environmental sounds, exhibits an auditory startle reaction, or turns the head to one side during conversation. The individual may report the presence of ringing in the ears, whistling, buzzing, or, in some instances, a roaring sensation in the ear. The latter is often accompanied by a sense of oral fullness and fluctuating hearing loss.

Cognition

Evaluation of cognition begins with assessment of orientation to person, place, time, and date. These questions are simply asked; however, the evaluator's name should not be used as a reference point. Rather, the name of an individual more familiar to the injured person should be selected.

The presence of attentional deficits can be determined either by observation or by interview with other professionals involved with the individual. An attempt should be made to determine if the individual's ability to persist with a task (persistence) is better or worse than the individual's ability to persist with mental activities (concentration). It is important to discern a difference, if any, between these two types of attentional tasks.[47,48]

Further investigation into attentional skills can be conducted by evaluation of whether an individual is able to change between activities efficiently and without a loss of information. Some individuals will be unable to change from one activity to another and exhibit perseverative tendencies. Others may be able to change between activities but do so slowly and lose information in the process. Finally, the evaluator should attempt to determine whether the individual is able to demonstrate vigilance by screening large amounts of information for a target stimulus.

Evaluation of very brief attentional store mechanisms, such as iconic (visual) and echoic (auditory), can be easily undertaken in the scope of a field evaluation. The examiner can prepare cards, as demonstrated in Appendix 22-B, for presentation of iconic store stimuli. The presentation of several 3 × 5 cards with three rows of three letters each[49] can be utilized, presenting each card briefly. Examiners should note that the card is presented anywhere from 2 to 5 seconds and, following presentation and removal of the card from sight, examiners indicate which row they would like the person to recall. As the examiner goes through various cards, the row requested should be chosen randomly and the accuracy of response noted. Line recall should be somewhere in the neighborhood of 75% and card recall in the neighborhood of 90% with a small amount of rehearsal. Echoic store can be evaluated by the presentation of randomly presented numbers, 0 to 9. Normal performance is in the neighborhood of six to seven numbers forward recall and four to five numbers backward recall.[50] The task can be further complicated by asking the person to order presented numbers from largest to smallest, thereby assessing both immediate recall and working memory.

Central to the processes of cognition is an individual's ability to identify perceptual attributes of objects and events in their environment.[47] The evaluator should attempt to discern the individual's fluency with this task by presenting up to three objects and asking the individual to provide a description. The examiner can model the description or can enumerate the variables desired, such as color, size, weight, shape, function, detail, texture, and construction. The total time required and the spontaneity of response, once the task is demonstrated, should be noted. The degree to which the evaluator needs to assist the individual in coming up with features should be noted. In order, then, to undertake this evaluation, the examiner might describe an object to the patient using the eight previously detailed features. A pencil could be 5 inches long; ⅜ of an inch in diameter; hexagonal in shape; yellow, pointed, or cylindrical; weigh approximately ½ ounce; be constructed of wood; have a lead

point or rubber eraser; and be used for writing. The individual is asked to carry out a similar description with up to three objects. This task should be able to be completed in less than 30 seconds per object, and notation of any perseverative response should be made. Of particular interest is whether an individual focuses on the object's function versus description of how the object is constructed.

Next, the evaluator should determine the degree to which the individual is able to use perceptual features to categorize.[51,52] This can be done with objects that are common and within the environment. It may be necessary to model the task for the individual. The evaluator should observe if the individual is able to categorize and determine which methods and techniques are used for categorization (see Chapter 19). As part of the evaluation of categorization, the examiner should attempt to determine if the individual can decide which items do not belong in an examiner-defined category. Use of real objects allows the examiner to create a group of objects that share a perceptual feature and to determine if the individual can decide what attribute is shared by all of the objects. For example, grouping of four or five metal objects should elicit a response that all the objects are made of the same material or of metals. Next, the evaluator should determine if the individual can decide which objects do not belong in a particular category.[51] The evaluator can determine if the person can extend categorical boundaries by asking questions such as "Can a chair be used as a ladder?" followed up by a request for a description of how this could be undertaken. Individuals who are very concrete and unable to extend categorical boundaries will answer the question in the negative. If an individual answers the question in the affirmative, the evaluator should determine whether the response is a randomly selected one or, in fact, is based upon sound reasoning. The intention is to identify the ability to alter the function of an object to an acharacteristic function based upon a particular feature. In the pencil example, the pencil could be used as a lever or as a weapon. The examiner can show the person an object and ask him or her to name three other objects not currently in the room that share a named feature with the one being shown, again noting responses, time to complete, and reasonableness of responses. Repetitive responses are not acceptable, and the patient should be encouraged to come up with novel responses.

Proverb interpretation can be undertaken to determine the degree to which an individual is functioning at an abstract reasoning level. Additionally, drawing a floor plan of the room in which the individual is sitting, including windows, walls, doors, and placement of furniture as well as a floor plan of the place where the individual lives can provide additional insight into visual perceptual skills as well as abstraction capabilities. In the instance in which the proverb is literally interpreted, it becomes apparent that the individual is functioning at a fairly concrete level. Floor plan execution and proverb interpretation can yield information about the individual's ability for planning, sequencing, cognitive distance,[47] visual imagery, and visual praxis.[53]

The ability to sequence can be evaluated by asking the individual to go through a detailed description of how to change a tire or bake a cake or some other gender- and experience-appropriate example. In a somewhat similar vein, problem solving can be evaluated by asking the individual what he or she would do in the event of a given scenario. One such example might be "What would you do if you came home and found a family member lying on the floor, unconscious, and bleeding heavily from a deep cut on the arm?" Acceptable responses should be noted as well as the time required to provide those responses. Once an acceptable response is obtained, the examiner adds a complication, such as being unable to awaken the person. A logical response might be that he or she would then call for help. The next complication added would be that the telephone does not work. A logical response to this complication might be to leave the individual and go to a neighbor's for help. Finally, the complication that the neighbors are not home can be provided. Some individuals will become quite frustrated with these task complications; others will provide unique and unrealistic responses to the complications, and still others will be able to provide a reasonable response to the complications. The response pattern should be noted as well as the time to respond.

Next, it is important to evaluate whether learning is rule-governed or nonrule-governed.[54] A deck of cards can be utilized to evaluate an individual's abilities in this regard. First, the cards are slowly dealt, face up, into two piles, which are separated on the basis of whether they are black or red. The individual is asked to tell the examiner the rule the examiner is using to place a card in either pile. The individual should be able to identify a rule within five to 10 cards per pile. If the individual is able to identify the rule properly, the examiner should continue by simply changing the pile into which the red cards and black cards are delivered (to the converse pile). Again, the individual should be able to tell the examiner that the rule has changed and what the new rule is. This is an evaluation of a "reversal shift" capability. The testing progresses with the examiner changing the rule entirely, placing face cards in one pile and nonface cards in the other. Again, determination of the change in rule and the nature of the rule is the target for this "nonreversal shift" activity. Care should be taken to evaluate the level of capability and/or frustration present during this task, and the task is discontinued should the individual be unable to complete the task or become frustrated with it. Previous administration of the Wisconsin Card Sort may provide the information that can be obtained from this procedure. Whether the individual is a reflective thinker or has an impulsive thought style should be evaluated and noted as cognitive tempo.[47] Speed of processing should likewise be evaluated.

Through much of the evaluation of cognition, the examiner can rely both on formalized evaluative procedures that might have been undertaken by professionals involved in the case and by observation of the individual's behavioral interaction with the environment and individuals in it. In this method, behavior is used as a representation of cognition.[55]

Education

The educational history of the individual should be obtained by interview with family as well as a review of academic records when possible. Those individuals who are in the process of completing or have completed high school may have academic records available to them personally. In any event, academic records can be requested of grade school and high school institutions and should be reviewed to gain insight into both academic performance and the possibility of previous observations or notations regarding injuries, attentional deficits, learning disabilities, or behavior problems.

All too often, a formal or informal academic skills evaluation is absent from a rehabilitative evaluation. In many instances, these areas are relegated to the speech pathologist or occupational therapist. In some specialized facilities, however, educational specialists are utilized to evaluate and remediate these skill sets.

In a field evaluation, a cursory look at mathematics, reading, writing, money management, and telephone skills is in order. For mathematics, the individual's ability should be evaluated to count with a random number of objects; add and subtract with either objects or without; identify sizes; write number symbols up to 100; count by twos, fives, and 10s up to 50; add and subtract without renaming up to three columns; add and subtract with renaming up to three columns; multiply one digit by one digit; multiply two digits by one digit; distinguish the value of a decimal fraction compared to a whole number; and find a percentage of a whole number. Reading skills, such as the ability to recognize random letters in the alphabet, read simple sight words, read functional sources (e.g., labels, newspapers, signs), and answer three comprehension questions about material read from a functional source, should be evaluated. Spelling and writing skills can be evaluated by asking individuals to write any given letter of the alphabet, copy a sentence, write two or three sentences about themselves, and spell two of four words at a sixth-grade reading level (i.e., direction, activity, vegetable, gentle).

A history should be taken pertaining to money management skills. It should be determined who managed money in the family prior to injury and the extent to which the injured individual participated in those activities. It should include experience with the management of real money, such as coin identification and making change, as well as whether the individual utilized a checkbook and how he or she managed the checking account. Finally, telephone skills can be evaluated by asking the individual to dial a number, determining whether the appropriate communicative techniques are utilized for the telephone, whether the individual is aware of emergency phone skills, and whether the individual is able to use a telephone directory. Discussion regarding money management skills with the family will allow determination of whether responsibilities have been given over to a family member or caregiver since injury.

The evaluator may wish to bring along grade-level, standardized math and reading exercises and problems to be used in the evaluation. Care should be taken not to assume capabilities not demonstrated. It is often tempting, based upon an individual's educational or vocational experience or, sometimes, based upon their linguistic skills, to forgo this portion of the evaluation.

Family

It should go without saying that collection of information pertaining to the family will be of great help in determining key players and their roles. It may be that the evaluation setting will not lend itself to a casual collection of this information or complete access to this information in that family members may or may not be present in all settings. In any event, the information should be collected, either by direct interview or telephone interview. The individual's marital status and prior experience with marriage or divorce should be discerned. Previous spouse or partner names and dates of marriages or domestic partnerships should be collected. All children from current and/or former marriages should be identified by name and age. Siblings, also, should be identified by name, age, and location. It is often helpful to attempt to discern siblings' occupational endeavors. These individuals may be quite insightful during treatment, may have worked in similar or identical fields and be helpful in identification of vocational aptitudes and skills, and may represent potential vocational placement options following completion of the medical rehabilitation. The parents' names, ages, locations, occupations, and marital status should be obtained as well.

Of greatest interest is the family's education and awareness of the diagnosis, individual deficit areas, and knowledge of the short- and long-term outlook for their family member. Often, families report that they feel quite at a loss to predict a longer-term outcome for the injured individual or themselves although they may have been given access to some information.[34] Reviewing the evaluation findings with the family, in detail, will both serve as an educational opportunity and an opportunity to determine gaps in their knowledge and provide education. Many families report a frustration with the lack of information and a coincidental relief when an evaluator can answer their questions, either about past, current, or future events. The evaluator will be interested to know whether the family has had counseling or is currently involved in counseling. Additionally, discharge options should be discussed with the family, determining their wish to be involved, their ability to be involved, and the degree of involvement they wish to have.

Conservatorship or guardianship issues can be quite varied from state to state and circumstance to circumstance—that is to say, some individuals may have no guardianship or conservatorship proceedings involved in their case. Others, however, may have a conservatorship over finance, a conservatorship over person, a conservatorship over both, a power of attorney arrangement, or some other arrangement.

Likewise, some individuals may not have any of these in place, and the evaluator may be in a position to advise that these matters be considered with the family's legal counsel. Family members are often poorly informed regarding the role of guardianship or conservatorship proceedings that may have been undertaken or may have been recommended. Consequently, it is always a good policy to obtain copies of any conservatorship or guardianship proceedings so that the evaluator and/or treating facility can be aware of the nature of the proceedings and the impact upon the individual's rights and liberties those proceedings may or may not have.

Occupational/physical therapy

Investigation of occupational and physical therapy status should begin with a review of the patient's treatment history and discussion with any currently involved professionals in these disciplines. Current information provided by these professionals can truncate the evaluation time and with no compromise of accuracy. Active and passive range of motion is of interest in the upper and lower extremities, head and neck, and trunk. These can be directly assessed or observed as the individual moves in the environment. Likewise, strength in the upper and lower extremities as well as head, neck, and trunk should be determined. The evaluator can note functional capabilities or can proceed through formal strength grading by physical examination. Sensation and proprioception should be evaluated. Comments regarding overall muscle endurance as well as cardiopulmonary endurance should be provided. Of interest in sensation testing is appreciation to light touch, to touch discrimination, and temperature differentiation in all four extremities. Facial sensation is discussed under the speech pathology section of this chapter. Likewise, proprioceptive awareness of the upper and lower extremities should be evaluated. When evaluating stereognosis, the evaluator should be careful that the individual does not see the object being placed in either hand. As the individual names the object, care should again be taken to note whether naming difficulties are present in both hands or only in the left hand. A deficit in stereognostic naming in the left hand may point to a callosal lesion.[56] If language impairment is present, the evaluator may ask the individual to identify the object he or she was holding from a group of objects.

The presence or absence of clonus in the upper and lower extremities should be noted. The evaluator is interested in fine motor coordination and dexterity. This can be observed through direct assessment, object manipulation, or finger-to-thumb opposition, progressing through each of the four fingers. Gross motor skills, such as the ability to roll from a supine to prone position and back, assume a quadruped position, assume tall kneeling, assume half kneeling, and stand from a half-kneeling position, will be important to the physical therapist. The individual's ability for transfers should be assessed as indicated from floor to chair or wheelchair, from wheelchair to chair, wheelchair to bed, bed to wheelchair, wheelchair to car, and wheelchair to toilet.

Balance should be evaluated for both sitting and standing, if possible. The evaluator can assess an individual's abilities for challenged and unchallenged sitting and standing balance, one-foot balance, and heel-toe walking. Weight shift during ambulation should be noted as well as posture, both sitting and standing. Gait should be evaluated for pace, required devices (such as orthotics, canes, walkers, etc.), trunk rotation, and reciprocal arm swing and should include smooth and uneven surfaces. If the individual requires a wheelchair, the type of wheelchair should be noted.

Individuals who are able to ambulate may yet require evaluation of balance. Care should be taken to guard against falls while testing vestibular function. The ability to walk does not preclude vestibular dysfunction that may be subtle and identified only upon testing. Evaluation of vestibular sensitivity should include review of complaints of headaches, nausea, vomiting, dizziness, lightheadedness, or a feeling of imbalance. Historical information may point to vestibular dysfunction, such as falls that occurred in low light conditions, loss of balance in the shower or while dressing or playing with the children, reliance upon night-lights, a feeling of imbalance, fear of heights or stairs, or discomfort or motion sickness following car rides or activities that require plane changes. The evaluator may wish to conduct a marching-in-place exercise with and without vision or other vestibular tests the evaluator may be comfortable with (see Chapter 6). Walking in a straight line, forward and backward, with eyes open and eyes closed can help to identify vestibular involvement. Deviation will be toward the side of involvement.[57] Of course, care must be taken to provide for proper safety precautions in guarding the person from falls with any balance or coordination testing. These activities should not be undertaken without proper training. Cerebellar testing can be done by heel-to-shin maneuver, finger-to-nose maneuver, and reciprocal alternating movements of the upper extremities.

The ability to complete activities of daily living (ADL) is of great interest. This should include hygiene, toileting, dressing, grooming, feeding, meal planning, shopping, meal preparation, laundry, and household cleaning. The degree to which the individual participates in these activities, the level of independence exercised, and the degree to which the individual participated in these activities prior to injury will all be important. Part and parcel to the evaluation of ADL skills is a review of the individual's typical daily routine. This should simply include a description of the individual's time to arise and all activities generally engaged in throughout the day until bedtime. Careful evaluation of the person's ability to initiate tasks as either part of routine or apart from routine should be conducted.[58] Essentially, the evaluator needs to construct a conception of the individual's daily and/or weekly schedule of activities. This should be contrasted to the daily or weekly schedule of activities the individual engaged in prior to injury. Driving habits prior to injury can be discussed as a part of this undertaking, and

the individual's ability to drive following the injury should be documented. States have different requirements regarding reporting to their motor vehicle departments, and the evaluator should be aware of those reporting requirements and/or whether the individual's injury or seizure condition, if present, has been reported. Finally, it is advisable to tell the patient and family that driving should not be undertaken until the individual is fully and carefully evaluated for visual, vestibular, motor, and cognitive capacity to drive safely.

Evaluation of gustation and olfaction is not often done. The evaluator may wish to carry a standard set of scratch and sniff patches to test olfaction. The presence of deficits in olfaction is fairly common following TBI[59] and should be suspected when the individual suffers weight loss, loss of appetite, or diminished meal volume consumption. Likewise, these same behaviors may point to difficulties with dentition and/or swallowing.

Psychosocial

Among the many areas TBI impacts in a person's life, perhaps none can be more profound than the changes in personality that are attributed to TBI by injured individuals, their families, and their friends.[34] A reasonable goal for rehabilitation is to attempt to return the individual to his or her preinjury lifestyle as much as possible. To that end, it becomes quite important to understand the individual's personal history. Information such as where the individual was born and raised, how frequently he or she moved, a military service history, social history, and religious affiliation will provide great insight into preinjury personality.

An evaluation of the individual's ability to describe his or her deficits and limitations should be conducted. The evaluator should attempt to discern how comprehensively the individual can describe his or her deficits and the degree of assistance needed to do so. Difficulties in acknowledgment or acceptance of disability should be identified, documented, and described. These skills can bear significantly on outcome and need to be recognized and treated early.[60] The individual may have difficulty due to cognitive processing problems, denial, rationalization, projection, repression, suppression, displacement, sublimation, or regression. The evaluator should obtain an idea of the individual's self-concept. How does the individual see himself? Does the individual demonstrate a consistency of self from preinjury to current status? Does the individual see himself as others do? Finally, the evaluator should attempt to determine the impact of the injury on self-esteem.

It is important to attempt to determine the degree to which the family is supportive of the individual, is understanding of the individual's deficits and limitations, and is able to participate in a rehabilitative milieu. Problem areas in the family should be identified, in particular, as they may impact the rehabilitative undertaking. A similar approach should be taken with friends, attempting to determine the quality and quantity of visitations or interactions.

The preinjury personality may have been more formally assessed somewhere in the individual's treatment. Formalized testing and dates as well as report summarization should be included in the evaluation. Additionally, the family's characterization of the preinjury personality and the individual's characterization should be reported. Information about membership in organizations, hobbies, recreational interests, preinjury goals, and current goals should be collected. The evaluator will need to request information regarding social and legal history. Results of formal neuropsychological and/or psychological testing should be reported with the dates of testing, the tests administered, and the findings.

Discussion of sexuality may be conducted either in the psychosocial portion of the evaluation or in the medical portion. The evaluator should attempt to discern the individual's ability to engage in various levels of social interaction and maintenance of social boundaries. Family may be best able to provide an historical reference to the person's expression of sexuality prior to injury. This should be compared to behavior following injury. It is important to attempt to determine whether emotional and sexual intimacy, libido, or ability to perform have been altered or impaired since injury.

TBI often impacts an individual's ability to handle frustration or to engage in socially appropriate behaviors. These deficits may manifest in impulsive anger, verbal aggression, physical aggression, or in behavioral manifestations that are outside of societal norms. The evaluator must note episodes of impulsive anger, frustration, verbal aggression, physical aggression, and any behaviors that have been noted to be problematic. The individual or family should be able to provide insight into coping mechanisms prior to injury and may be able to provide insight into current strategies. It is important to evaluate how the individual shows frustration; whether he or she engages in withdrawal or aggression; and whether there is anxiety, nervousness, psychosomatic complaint, lability, or depression. Information may be available regarding previous psychological or psychiatric treatment. The evaluator should discern whether paranoia, hallucinations, delusions, addictions, depression, regression, or psychosomatic complaints have been noted or observed. The individual's motivational capabilities should be identified, both for those areas in which the individual seems highly motivated or, perhaps, "overly motivated," as well as a lack of motivation or initiation.

The involvement of psychiatry in the management of an individual with TBI should be noted along with medications prescribed and their relative success in achieving change in targeted behaviors or function. Any progression in behavior should be noted along with all medication progression given that some behavioral manifestations may arise from iatrogenic complications of pharmacological interventions.

Speech/language pathology

Deficits of interest in speech/language pathology following TBI are typically in the areas of cognition, motor speech

disorders, dysphagia, language disorders, fluency, and voice. As part of the evaluation of motor speech disorders and dysphagia, an oral peripheral examination is undertaken. Observation of the facial symmetry, at rest and in movement, is undertaken to determine whether any asymmetries are present. Facial sensation should be evaluated at all three branches of cranial nerve V[45,46] as this nerve is particularly vulnerable to injury in the temporal region where it exits the skull. The mandibular rest position is noted as well as the ability to extend and lateralize the mandible and any joint pain. Position of the tongue at rest and in various maneuvers is noted, again, with an expectation for no tremor, no fasciculations, and symmetry of movement. An oral peripheral examination form is attached in Appendix 22-C of this chapter. It is not likely that the evaluator will conduct an otoscopic examination; however, otoscopic examination has probably been performed, and the results should be noted. Likewise, swallowing is most generally evaluated at the acute level, and the most recent swallowing evaluation as well as the history of evaluation of dysphagia should be noted. The evaluator should look for consistency in the management of foods, liquids, secretions, and radiographic evaluation of swallowing. The examiner can undertake a quick apraxia assessment by asking the individual to undertake several activities without demonstrating those activities. These include 1) stick out your tongue, 2) blow, 3) show me your teeth, 4) pucker your lips, 5) bite your lower lip, 6) whistle, 7) lick your lips, 8) clear your throat, 9) cough, 10) smile, and 11) puff your cheeks. Articulatory agility or the ability to make various speech sounds clearly and quickly should be noted. Throughout the evaluation, the individual's ability to maintain topic can be determined.[61,62] Any difficulties with fluency (stuttering) should also be noted. Should a fluency disorder be present, the evaluator should determine if this preexisted the injury. Voice can be characterized as breathy, nasal, hoarse, soft, or loud. A nasal quality in voice may suggest a velopharyngeal paresis.[63] Evaluation of intonational changes in conversation should be included as their absence can materially impact communicative intent and success.[64] History of endotracheal should be noted, and an attempt should be made to determine pulmonary capacity.

TBI does not generally result in pure receptive or expressive aphasias as are often demonstrated in cerebral vascular accidents (CVA). However, evaluation of expressive and receptive language skills should be undertaken and/or test results reported. Most frequently observed are difficulties with anomia, paraphasias, and neologisms. A paraphasia is a whole word substitution, such as "tar" for "car." Neologisms are nonsense words or syllables.[65,66] Finally, the ability to communicate intent should be assessed with a description of the means utilized to communicate.

Vision

A visual evaluation early after TBI is difficult to undertake and is, therefore, often postponed. Clearly, cranial nerve involvement (see Chapter 7) is often included in a neurological evaluation, and some work-up of visual perceptual skills may be available in the occupational therapy history. The evaluator should note whether the individual had prescriptive lenses prior to injury and for what purpose as well as whether those lenses are currently available and in use. Documentation of complaints of visual acuity should be included, and any formal ophthalmologic examination that has been undertaken should be reported with dates and results. Individuals may report difficulty seeing, blurred vision, double vision, changes in vision with fatigue, difficulty reading, and, in some instances, may report image persistence (being able to see an object after looking away from it) or lack of recognition of familiar objects, places, or persons.[67,68] Some of these reports may not be spontaneous and may require the evaluator's active investigation.

The evaluator can test visual fields to confrontation and can evaluate ocular motility and gaze convergence. Evaluation of visual fields is conducted by covering one eye and moving an object from the ear forward into the lateral field of the uncovered eye. The person is asked to maintain a straight-ahead focus and indicate the earliest point at which the object comes into the peripheral field of vision. The maneuver is repeated from over the head to check superior quadrants, under the chin to evaluate inferior quadrants, and the opposite side of the head to the covered eye to evaluate nasal fields. The entire process is repeated for the other eye. Evaluation of ocular motility is performed by asking the person to track with eyes only the movement of an object that is moved in front of the person from left to right to left, up and down, and in a circle. The evaluator is looking for smooth and convergent movements of the eyes without overshooting or jerky movement, which could imply brain stem involvement of cranial nerves III, IV, VI, or VIII.[69,70] Finally, behavioral observation may help to discern the presence of visual field cuts or neglect as when an individual bumps into objects or appears to miss information in the environment predominantly in a particular visual field or quadrant. Here again, it is important to advise the patient and family of any findings in visual fields as these particularly can impact driving and safety in ambulation in various environments.

Information about visual perceptual skills may be available from the occupational therapy department or from ophthalmologic or optometric evaluation. Of interest are depth perception, binocular or stereovision, visual figure-ground, visual praxis, and visual organization skills. The examiner may wish to carry subtests of standardized visual perceptual tests in order to investigate visual perceptual skills.

Productive activity/vocation

The individual's preinjury vocational endeavors should be chronicled in the evaluation. This consideration should be given to those whose primary productive activity was as a homemaker or as a volunteer worker. This should consist of a chronological review of at least the last 10 to 15 years of

productive activity or employment, complete with job position, companies, locations, and salaries. A complete history provides a great deal of information about an individual's work ethic, intellectual capability, social experience, and vocational experience. If large gaps in employment history are noted, reasons for unemployment should be determined. Likewise, if an individual has a history of frequent job changes and positions of short duration, reasons for those job changes should be listed. An individual who frequently changes jobs may have a history of inappropriate social skills as they pertain to job settings or difficulties with maintaining employment. By the same token, some professions, by their very nature, subject an individual to frequent changes in employer. Consequently, any conclusions drawn regarding an individual's work ethic, personality, or vocational history should be drawn from a comprehensive review of these factors. This section should culminate with the job held at the time of injury or the most recent position and salary. Families or injured individuals themselves may be able to provide insight into positions the individual disliked and liked as well as goals the individual had and/or has. The individual's goals for vocational involvement should be determined together with the family's goals and expectations. Finally, any vocational evaluation or testing that has been completed should be reported with dates and results.

REPORT PREPARATION

Appendix 22-A to this chapter and, indeed, the very format of this chapter, can be used in report preparation. Findings under each heading can be listed within their own subsection in a report; however, the most important section of the report is likely to be the "impressions and recommendations" section. This section of the report must be clear, concise, and able to answer most questions of most readers. Unfortunately, many varied professionals read reports, and it is not possible to anticipate all of those questions nor is it advisable. Thus, when the report is prepared, it should be prepared with the referral questions in mind, very clearly stated, and answered as clearly as possible in the "impressions and recommendations" section.

A good practice is to utilize a standardized scale reporting in an effort to quantify the individual's functioning status in a means that may be immediately understandable across treatment settings. Scales that allow this are the Disability Rating Scale, the Rancho Los Amigos Scale, the GCS, and the Functional Independence Measure. The level of disability should be characterized in terms of the scale or scales utilized. Note that not all scales are appropriate for all time points in which an evaluation may be conducted. The Functional Independence Measure, for example, is intended for use in acute and rehabilitation hospitalization settings.

The referral question should be posed and answered with a listing of factors that will positively influence attainment of any identified goals and factors that will impede attainment of those same goals. It is often best to list recommendations in a numbered fashion, and it may be helpful to both the preparer of the report and its reader if these recommendations follow the general outline of the report in order. Consequently, following the outline of this chapter, recommendations of a medical nature would be provided first, followed by audiometry, cognition, education, family, occupational and physical therapy, psychosocial, speech/language pathology, vision, productive activity/vocation, and impressions/recommendations.

The report should include whether the individual is an appropriate candidate for admission to a specific care setting or treatment setting if this question has been raised. The report should answer whether ongoing rehabilitative services are in order and the expected outcome of those services, if rendered, together with time and cost expectations. Again, this information should be provided only if requested as the primary purpose of the evaluation. Should the individual not be an appropriate candidate for a particular program, it is felt that the evaluator should attempt to provide alternate suggestions for the referral source, injured individual, and/or family. The report should conclude with information about how to contact the evaluator with questions or comments.

SUMMARY

The evaluation of a person with TBI poses considerable challenge to the professional. The evaluation is rarely complete enough, and time allotted for evaluation is all too often insufficient. In any evaluation, there will almost universally be more information needed than provided, and the art form to be realized is the successful collection of a maximal amount of information in the time allotted. The evaluator should develop a sense for which information is most important and germane and a routine within the treatment setting for a collection of information that may not have been available at the time the evaluation was conducted. The evaluation should be viewed as a preliminary venture that sets the stage for a team of professionals to become involved in more in-depth diagnostics and evaluations. Treatment plans that will subsequently be established will be preferentially or detrimentally impacted by the quality of this initial evaluation. It is this author's contention that allied health professionals in the field of TBI have an ethical responsibility to put forth the effort necessary to conduct a thorough, comprehensive, and accurate evaluation. That said, it is clear that there is strong desire to communicate information succinctly and efficiently. Characterizing the impact of a TBI on an individual is best done via prose; however, the time demands on many professionals in health care, case management, and payer communities preclude dependence upon prose reporting alone. The evaluator is challenged to find effective means to communicate vast amounts of information in a manner that properly depicts the complexity of the individual's condition for all concerned parties.

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APPENDIX 22-A: PATIENT EXAMINATION REPORT TEMPLATE

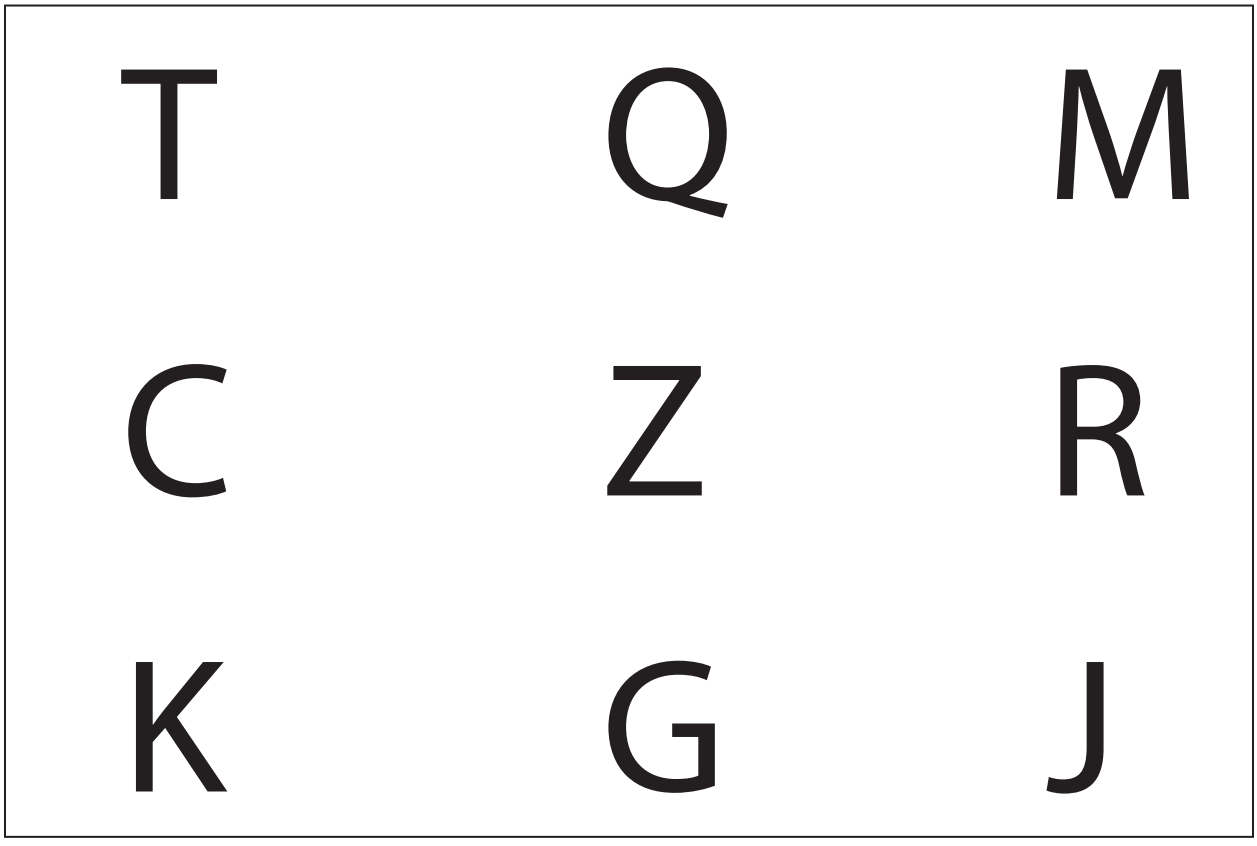
Client:	Xxxxxxxxxx
Age:	XX
Date of birth:	XXXXXXXXXX
Social security number:	000-00-0000
Date of injury:	XXXXXXXXXX
Carrier case manager:	XXXXXXXXXX
Claim no.:	XXXXXXXXXX
Reinsurance:	XXXXXXXXXX
	XXXXXXXXXX
	XXXXXXXXXX
Contact:	XXXXXXXXXX
	XXXXXXXXXX
	(000) 000-0000
Date of evaluation:	August 18, 1995
Date of report:	August 24, 1995

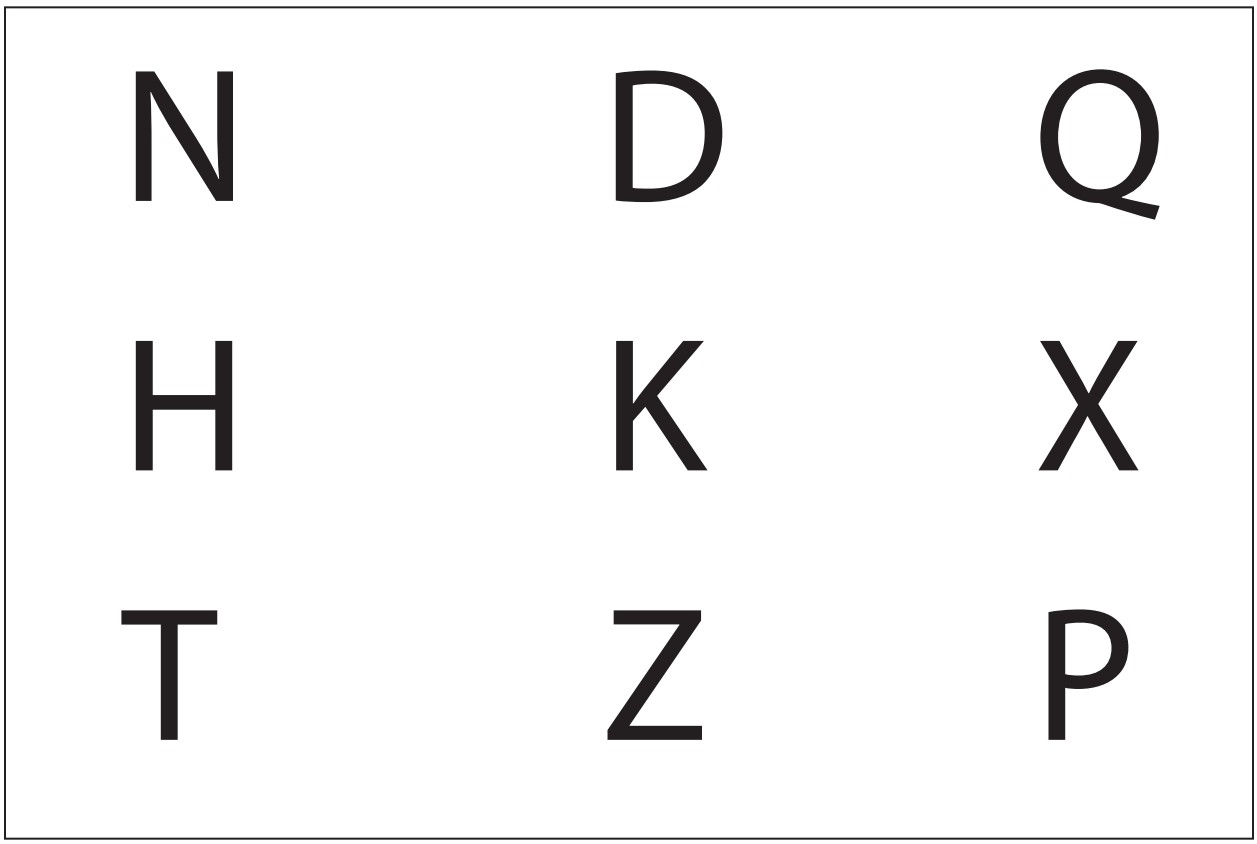
An onsite patient examination was conducted of Mr. Xxxxxx Xxxxxxxxx on August 18, 1995. The examination was conducted at the request and authorization of Mr. Xxxxxx Xxxxxxx, Assistant Vice President, Xxxxxxx Xxxxxxxxxxx Corporation. Present and/or interviewed during the examination were Mr. Xxxxxx Xxxxxxxxx, Ms. Xxxx Xxxxx, Mr. Xxxxxx Xxxxxxx, and Mrs. Xxxxx Xxxxxxxxx. The examination was conducted by Xxxx X. Xxxxxx, XX, XXX-XXX, XXX, Xxxxxxxxx Xxxxxxxx of Xxxxxx xxx Xxxxx Xxxxxx in Xxxxxxx, [state]. The examination was conducted in Dr. Xxxxx Xxxx'x office.

Medical history:
Audiometry:
Cognition:
Education:
Family:
Occupational/physical therapy:
Psychosocial:
Speech/language pathology:
Vision:
Vocation:
Vocational rehabilitation:
Impressions/recommendations:

Sincerely,
Name of organization
Name and credentials of examiner
Title of examiner

APPENDIX 22-B: ICONIC STORE CARDS

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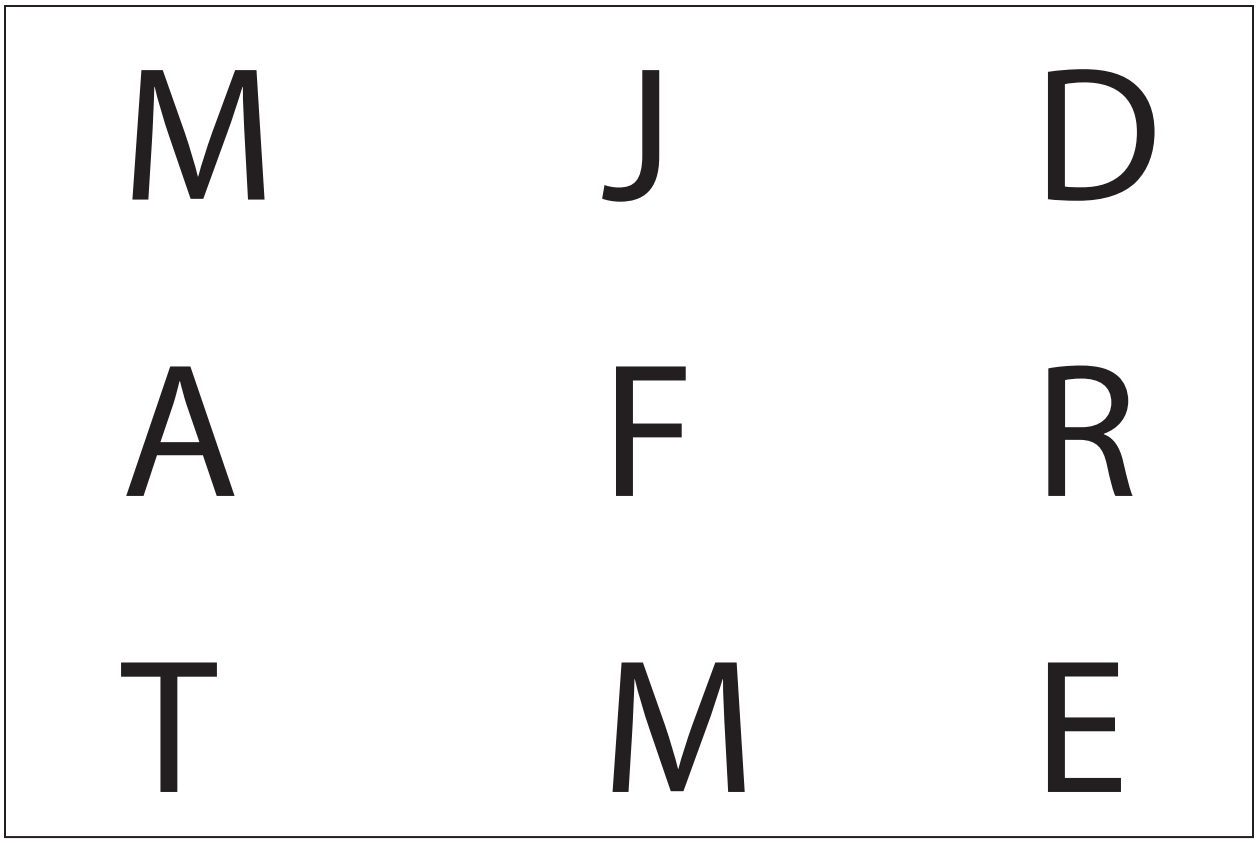
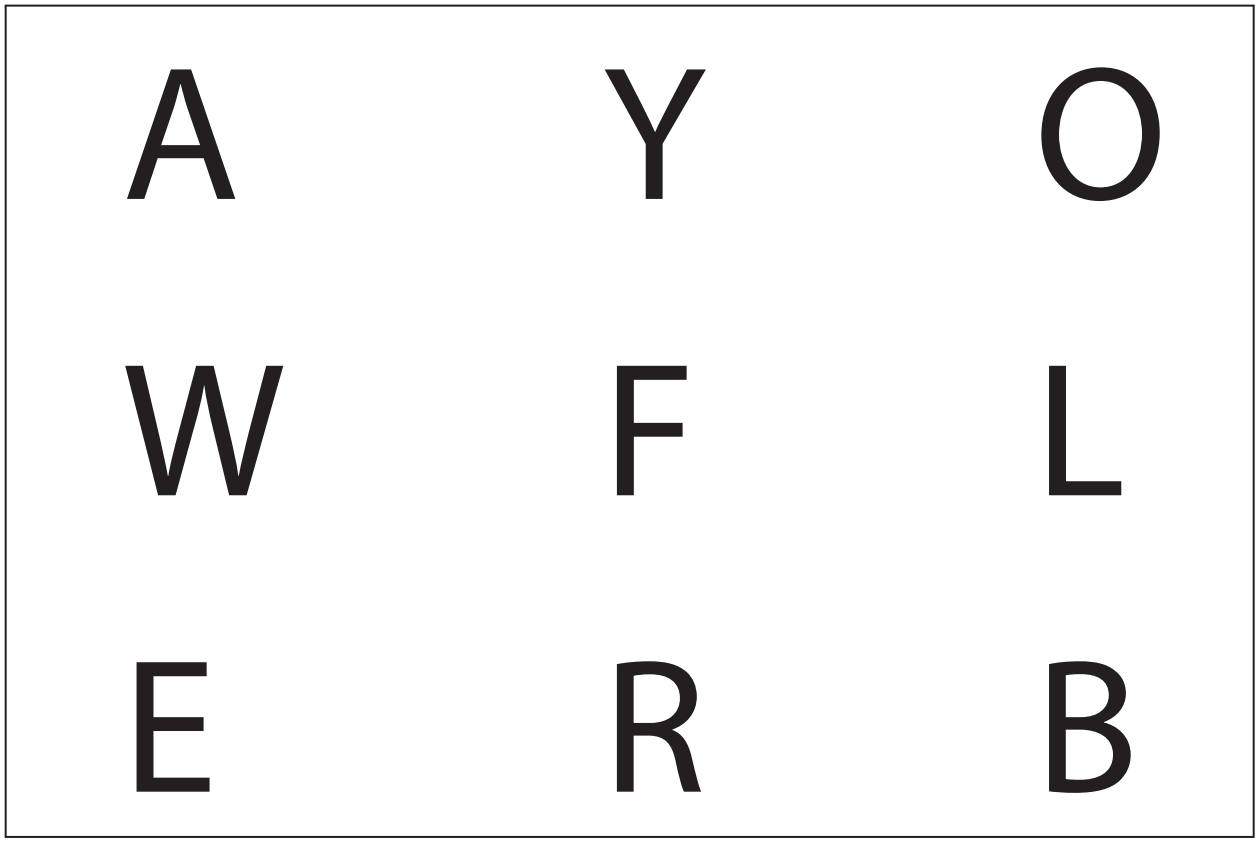
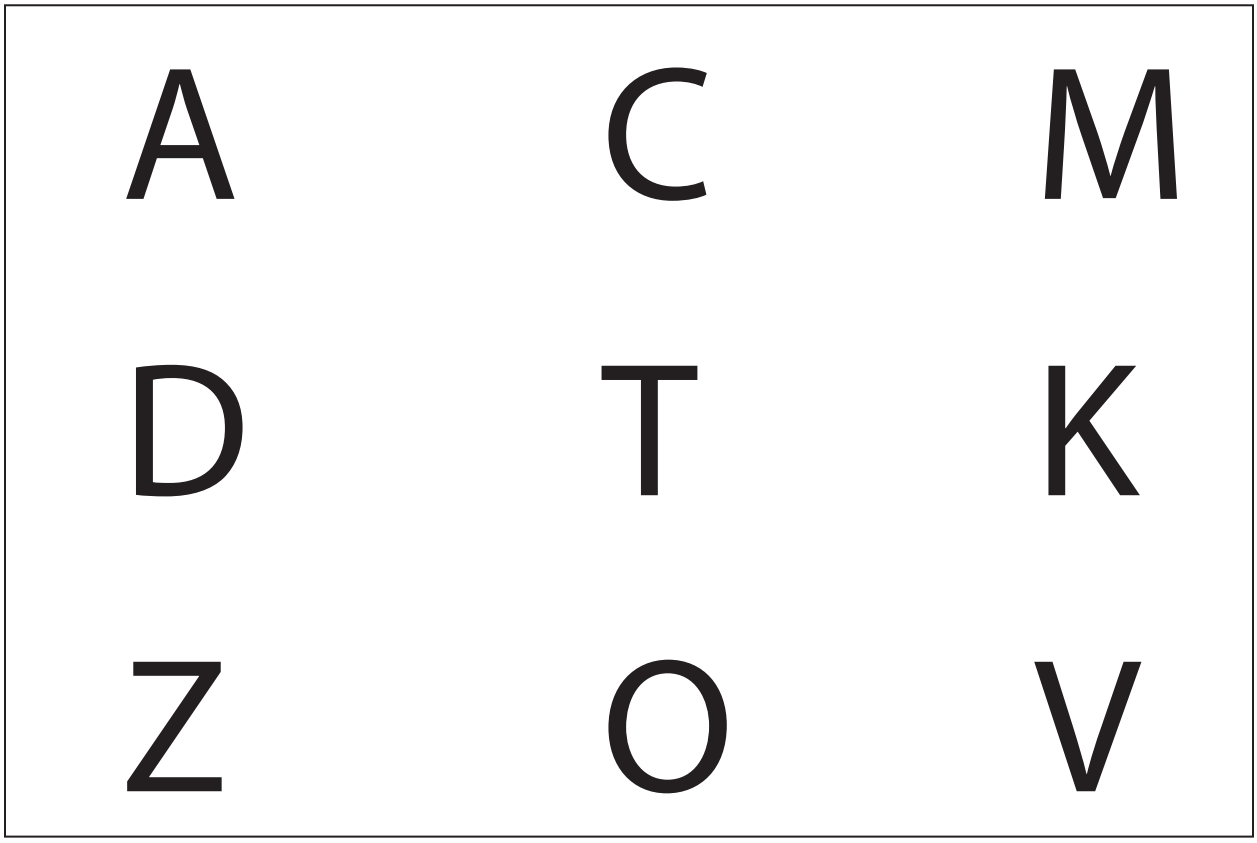
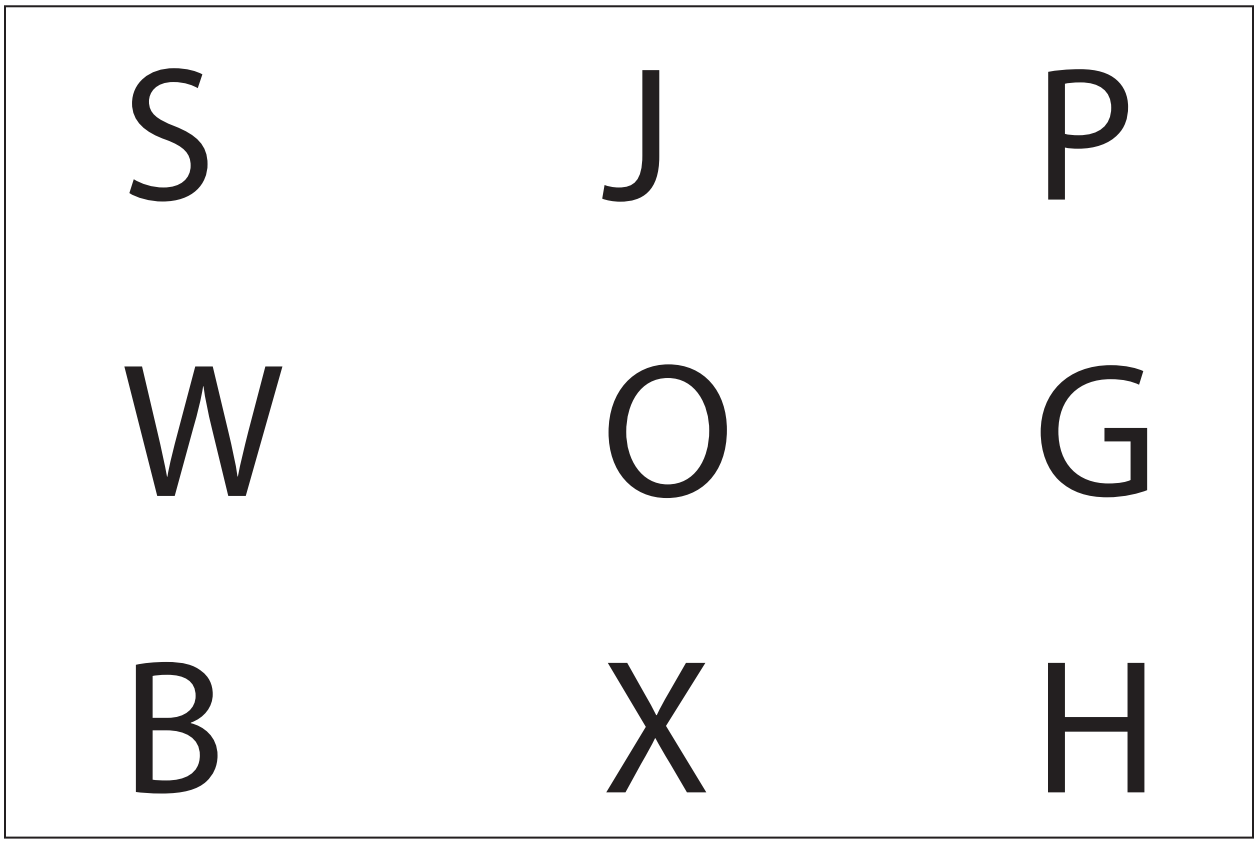
H K X
T Z P


M J D
A F R
T M E


A Y O
W F L
E R B


A C M
D T K
Z O V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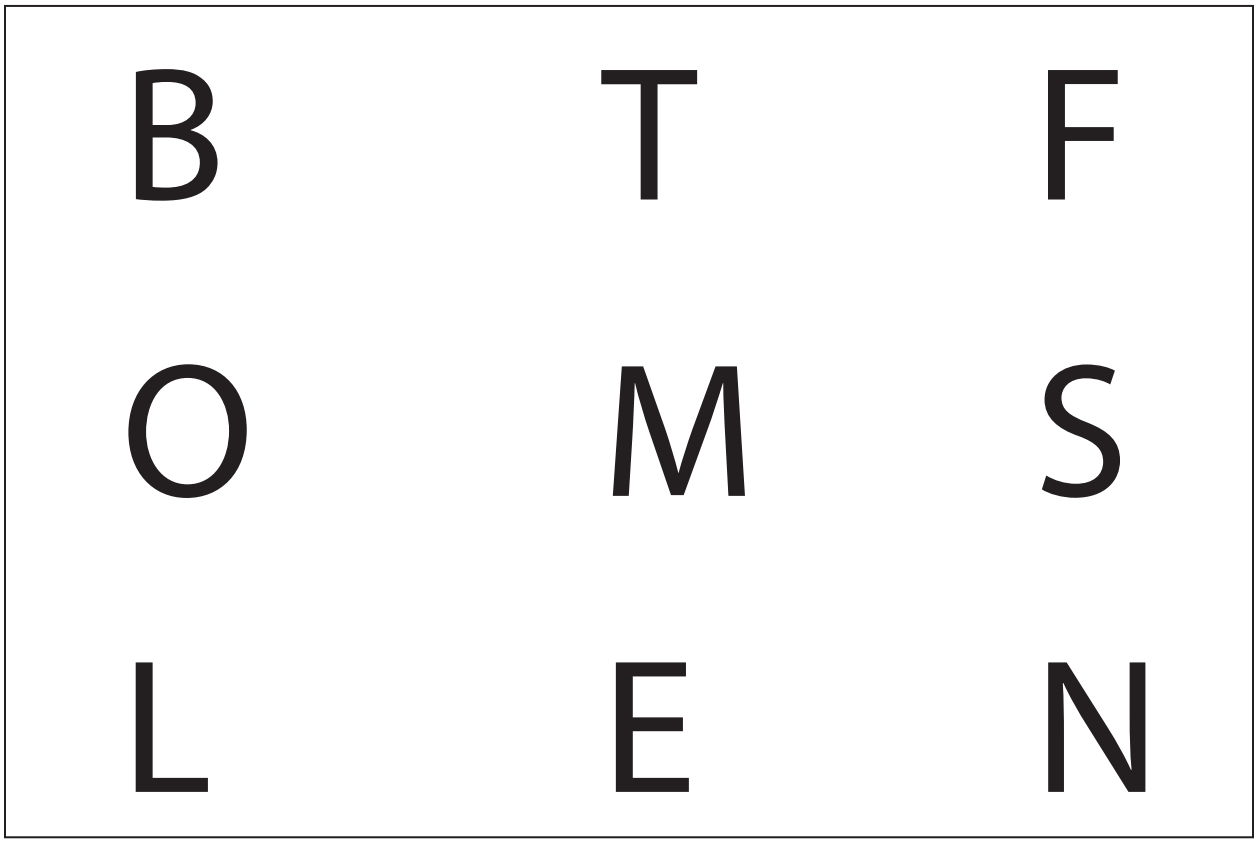
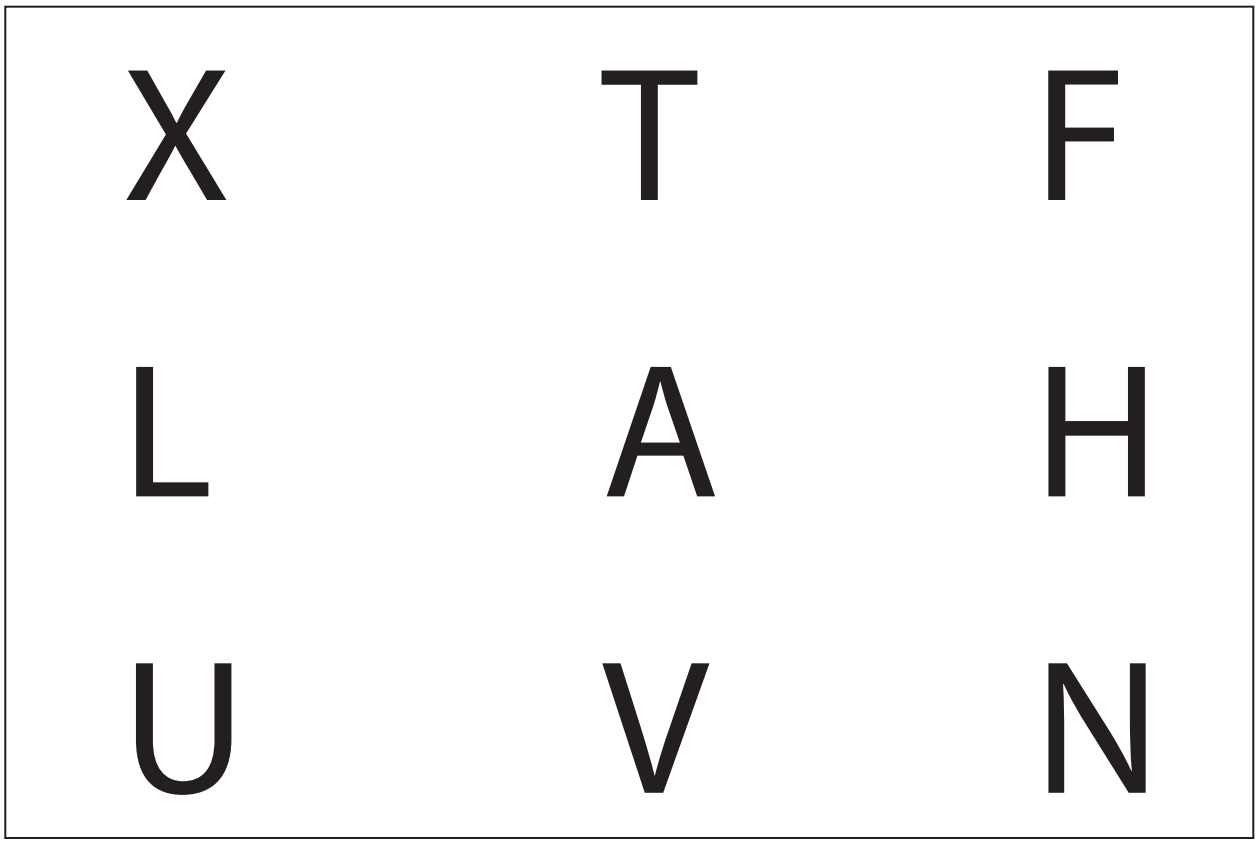
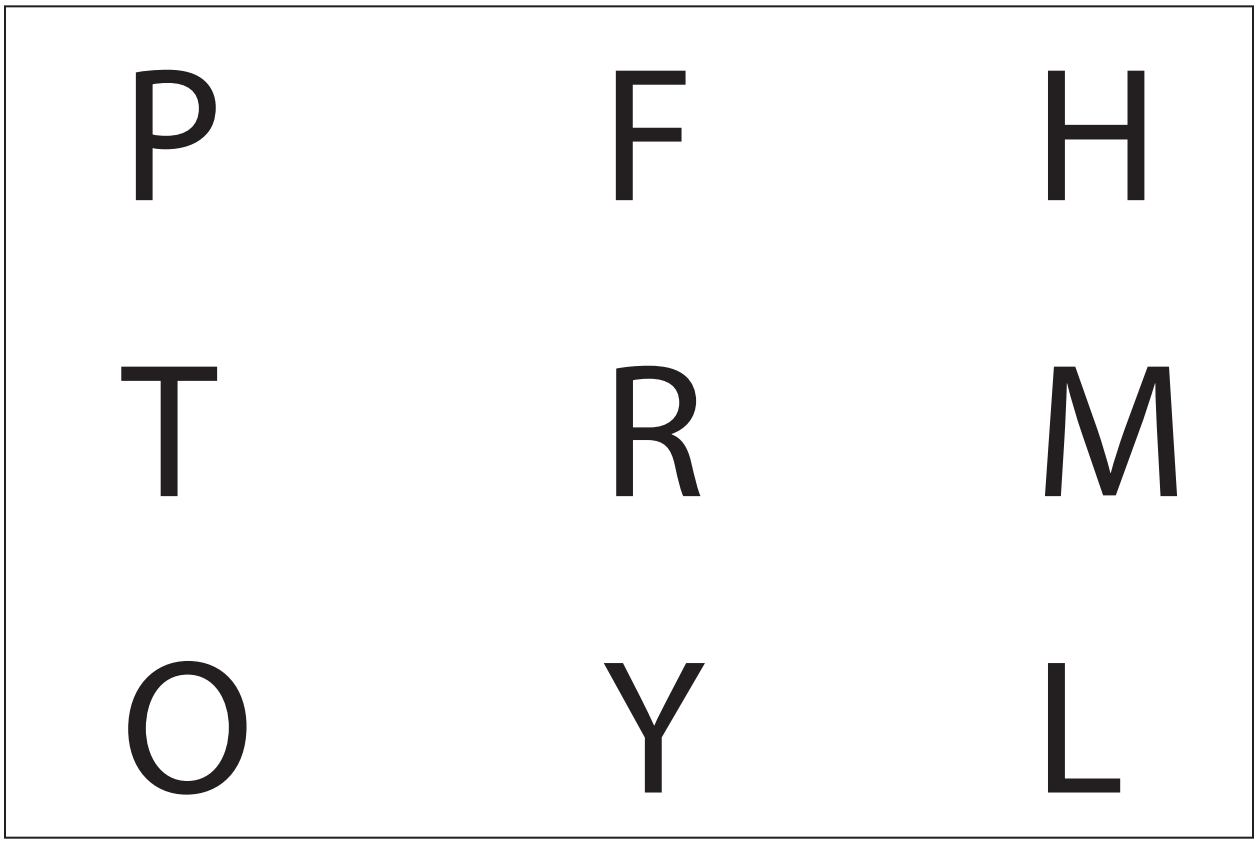
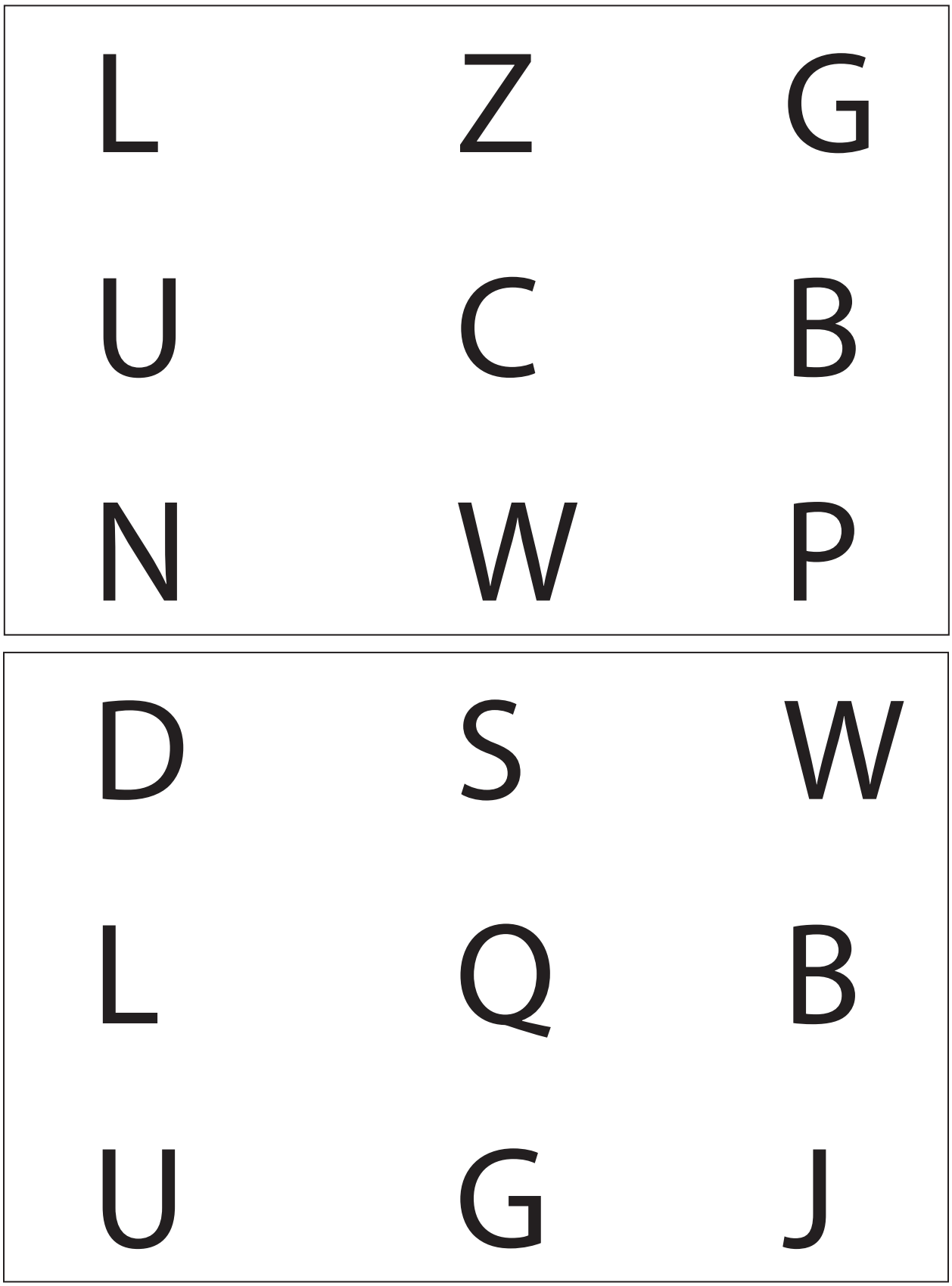
W O G
B X H


B T F
O M S
L E N


X T F
L A H
U V N


P F H
T R M
O Y L


L Z G
U C B
N W P
D S W
L Q B
U G J

APPENDIX 22-C: ORAL PERIPHERAL EVALUATION FORM

Client name		**Date**	
Facial symmetry			
Rest:	Normal	Right droop	Left droop
Smile:	Normal	Right weak	Left weak
Labial strength:	Normal	Weak	
Pucker:	Normal	Weak	
Facial sensation:	V 1	V 2	V 3
Mandible			
Rest position:	Normal	Low	
Jaw extension:	Normal	Right	Left
Jaw lateralization:	Normal	Right absent	Left absent
Resistive closure:	Normal	Weak right	Weak left
Tongue			
Rest:	Normal	Right atrophy	Left atrophy
Tremor:	Absent	Present	
Protrusions:	Normal	Right deviation	Left deviation
Fasciculations:	Absent	Present	
Protrusion strength:	Normal	Weak	
Elevation:	Normal	Weak	
Lateralization (in cheek):	Normal	Right weak	Left weak
Diadochokinetics:	Normal	Depressed	_____
Oral mucosa:	Normal	Lesion(s): Describe	_____
		Mass: Describe	_____
Velopharyngeal mechanism			
Rest:	Normal	Right droop	Left droop
Clefts:	Absent	Present	
Ah:	Normal	Right droop	Left droop
Hypernasality:	Yes	No	
Gag:	Absent	Present	

Hearing:_____

Swallowing: Liquids _____

Solids _____

Vital capacity: (three trials.)

Sustained phonation: ah_____ s_____ z_____

Apraxia battery

1. Stick out your tongue
2. Blow
3. Show me your teeth
4. Pucker your lips
5. Bite your lower lip
6. Whistle
7. Lick your lips
8. Clear your throat
9. Cough
10. Smile
11. Puff your cheeks

Dentition: Good repair Poor repair

(*Continued*)

Client name **Date**

Dentures: Maxillary Mandibular
Occlusion: Normal I II III
Describe _____

Corrective lenses: Yes No

Hearing aids: Yes No One or two
Type _____

Dysarthria: Yes No
Severity: Mild Moderate Severe

Apraxia: Yes No
Severity Mild Moderate Severe

Other: _____
_____
_____
_____

Smoking: Yes No How much? _____

Recommendations: _____
_____
_____

_____
Speech/Language Pathologist

23

Neuropsychology following brain injury: A pragmatic approach to outcomes, treatment, and applications

JAMES J. MAHONEY, III, STEPHANIE D. BAJO, ANTHONY P. DE MARCO, AND DONNA K. BROSHEK

INTRODUCTION

One of the most important components of a neuropsychological evaluation is identifying factors that may be contributing to a patient's symptom presentation. It is important for rehabilitation professionals to recognize that although patients may certainly have persisting cognitive deficits, psychological, personality, and psychosocial factors can also complicate recovery and treatment. This chapter provides a review of neurocognitive outcomes following traumatic brain injury (TBI) as well as highlighting several of the more commonly observed factors that may complicate recovery. More specifically, we focus on psychological contributions (both premorbid and postinjury), pain, sleep dysfunction, and substance abuse. Various forms of testing and treatments following brain injury are also described in detail. Finally, the utility of neuropsychology evaluations is discussed, including when to refer a patient for a comprehensive evaluation, a deconstruction of the neuropsychological report, suggested recommendations, the importance of providing patients and caregivers feedback and education.

NEUROPSYCHOLOGICAL OUTCOMES AND TREATMENT OF BRAIN INJURY

Neurocognitive sequelae and outcomes of brain injury

Neurocognitive and neurobehavioral symptoms are common sequelae of TBI across the severity spectrum. Over the past several decades, research efforts have focused on characterizing neurocognitive recovery trajectories and identifying predictors for poorer outcomes associated with TBI. Readers should bear in mind that neurocognitive outcome from brain injury is a somewhat controversial topic with often polarized views, especially in reference to injuries at the mild end of the spectrum. For instance, the operational definition of mild TBI/concussion, which has evolved dramatically over the years,[1] is quite broad, encompassing a wide variety of symptoms, such as "feeling dazed" following a head/brain injury to experiencing a loss of consciousness lasting less than 30 minutes. The heterogeneity in the definition of brain injury alone is enough

to engender methodological challenges within and across outcome studies.[2]

Across age ranges, the acute neurocognitive sequelae of mild TBI/concussion can include slowed information processing speed, inattention, executive dysfunction, and deficits in learning/memory. Within adolescents, there is evidence to support good neurocognitive recovery following a single mild TBI/concussion (several weeks to a few months). There is also evidence to suggest that prolonged symptoms are similar to those seen in same-aged peers with injuries other than those involving the head and/or brain, such as orthopedic injuries.[3,4] When compared to a cohort of collegiate athletes, studies have found that adolescent athletes may demonstrate a relatively prolonged recovery following a mild TBI/concussion[5–7]; however, objective difficulties persisting longer than 2 to 3 months following the injury are not common in pediatric samples although some may continue to report subjective concerns.[8] The prolonged recovery trajectory observed in adolescents may suggest that the developing brain is a vulnerable brain.[9,10] In adults, it is well understood that a majority of individuals who sustain a single or isolated mild TBI/concussion, regardless of the mechanism of injury, typically experience excellent recovery.[11] Neurocognitive deficits are transient, typically resolving within 10 days for athletes and within 1 to 3 months for trauma patients in a majority of cases.[12] This aligns nicely with animal models that have demonstrated a similar time period of neurometabolic dysfunction and stabilization following fluid percussion injury.[13] A very small subset of individuals, both adolescents and adults, will go on to experience postconcussive syndrome (PCS), a constellation of symptoms that is not specific to head and/or brain injury and one thought to be perpetuated more so by premorbid and comorbid factors (e.g., psychological factors) rather than the index mild TBI/concussive injury, especially as the time since injury grows[14,15]; it is important to note, however, that this assertion has been debated.[16–18] It is clear, however, that PCS is a complex entity that is likely maintained by the interplay of a number of different factors.[19]

When assessing and treating patients who have sustained brain injuries at the moderate-to-severe end of the continuum, the neurocognitive recovery trajectory becomes less clear and less predictable as the recovery process is more individual. As with mild TBI/concussion, the cognitive domains adversely impacted by moderate and severe brain injury can include learning and memory, language abilities, executive functioning, visuoperceptual abilities, attention/concentration, and motor functioning. Depending on the nature of the injury, deficits can be circumscribed to a particular cortical region or be more diffuse in nature. Deficits following moderate or severe brain injuries can also be transient, prolonged, or persistent. Dikmen and colleagues[20] illustrated a linear relationship between injury severity and the magnitude and the number of impaired cognitive domains, with very severe brain injuries resulting in diffuse cognitive impairment.[20] Moderate-to-severe brain injuries tend to be associated with cognitive deficits that last 6 months or longer postinjury, and this association appears to be moderated, to some degree, by the mechanism of injury (i.e., penetrating brain injury), volume of cerebral tissue loss, brain region affected by the injury, and premorbid intellectual functioning.[21] The majority of the neurocognitive recovery following a moderate-to-severe brain injury occurs within the first year with additional, albeit less dramatic, improvements observed during the second year postinjury when the recovery curve begins to plateau. In adolescents, the neurocognitive outcome following a moderate brain injury is similarly variable, but as expected, there is strong evidence to support that these youth tend to perform worse than counterparts with mild TBIs.[22] In a review of the literature, Lloyd and colleagues identified age at injury for pediatric patients, more specifically younger age, as a risk factor for both acute and long-term adverse outcomes, once again highlighting the susceptibility of the developing brain.

The association between brain injury and dementia has been of long-standing interest, and it has reemerged more recently. In adults receiving acute inpatient rehabilitation care, a recent epidemiological study found that, based on age, the largest proportion of individuals admitted for care secondary to brain injury was those within the 80+ age group.[23] This study also found that the risk of sustaining a brain injury secondary to falls (vs. motor vehicle accident or other mechanisms of injury) increased with age. Although older adults demonstrated a trend to sustain less severe brain injuries than their younger counterparts, they exhibited less improvement during the rehabilitation course.[23] The latter finding aligns with the research illustrating much older age as a risk factor for adverse outcomes and prolonged recovery following brain injuries of all severities.

In 1928, the term "punch-drunk syndrome" was utilized to describe persistent neurological deficits observed in boxers, typically characterized by memory impairment, disturbed speech, motor symptoms (e.g., tremor), difficulty with balance, and changes in personality.[24] The term "dementia pugilistica" was coined by Millspaugh in 1937, which he described as typically frequent and varying trauma from a comparatively insignificant abrasion, contusion, or laceration to compound fracture, brain concussion, loss of consciousness, coma, or death.[25] Both "punch-drunk syndrome" and "dementia pugilistica" were precursors to chronic traumatic encephalopathy (CTE), a neurodegenerative condition that has garnered much recent interest and attention in the mass media. The subsequent literature examining the association between brain injury and dementia-related disorders, including dementia due to Alzheimer's disease, has been inconsistent with some studies finding no link between the two disorders[26] while other researchers have found evidence in support of the association.[27–29] In a sample of retired professional American football players, Guskiewicz and colleagues[30] found an increased risk for mild cognitive impairment, a precursor to Alzheimer's disease, and other dementia-related syndromes among retirees who reported a history of repetitive concussive injuries.[30] Additionally,

among their retiree sample, there was a trend for an earlier age of onset of Alzheimer's disease than that typically reported in the American population. Turning an eye to the armed forces, in a recent retrospective cohort study examining the risk of dementia in older veterans, Barnes and colleagues found that, after controlling for potential confounders, veterans who had sustained a brain injury were 60% more likely to develop dementia when compared to veterans without a history of brain injury.[31] Additionally, as with the retired football players, onset of dementia was earlier in veterans with a history of brain injury by approximately 2 years. The magnitude of these findings was similar across various brain injury diagnoses and severity (e.g., intracranial injury with or without skull fracture, postconcussion syndrome, unspecified brain injury). In a more multifaceted theoretical explanation for the association between brain injury and dementia, Moretti and colleagues[32] postulated that the structural and functional changes associated with brain injury and normal aging interact to exacerbate cognitive decline in older adults. These interactions are mediated, however, by an individual's cognitive reserve and other factors (e.g., genetic predispositions, severity of the brain injury, medical history, education).[32]

Potential mechanisms of action accounting for the association between brain injury and increased risk for dementia have included structural changes, an accumulation of amyloid precursor protein and β-amyloid plaques, and tauopathy.[33] For example, CTE has been characterized as a tauopathy distinct from other neurodegenerative conditions.[34] Although the neuropathological findings have been reported to be distinct, the clinical phenotype of CTE remains unclear. Furthermore, the association between CTE and multiple concussive and/or subconcussive injuries has been only documented, at this point, largely through well-publicized anecdotal case studies.[35]

Confounding factors affecting outcomes

As mentioned earlier, neuropsychological evaluation is useful in identifying multiple factors that may be contributing to a patient's symptom presentation following brain injury. It is important for rehabilitation professionals to recognize that patients may certainly have persisting cognitive deficits but that psychological, personality, and psychosocial factors can also play a significant role in recovery or be key factors in a complicated or slow recovery. In the early 1990s, Kay and colleagues at the Rusk Institute of Rehabilitation Medicine proposed a neuropsychological model of functional disability after brain injury and identified multiple factors associated with functional disability.[36] These factors were neurological, physical, psychological, personality variables, psychosocial issues, and litigation. Their model illustrated that patients with brain injury may not only have neurological impairment but also peripheral injuries, pain, preexisting psychological or personal factors, and psychological reactions to injury, as well as personal and family stressors, including litigation. Although there is a robust literature on the role of litigation in symptom presentation, a review of litigation factors is beyond the scope of this chapter.[37] We review some of the most common confounding factors impacting recovery from brain injury, including psychological distress, pain (e.g., headache pain and pain due to peripheral injuries), sleep disturbance, and substance use.

PSYCHOLOGICAL FACTORS

Psychological disturbance is common following mild-to-severe brain injury. These emotional changes may be *de novo*, the result of adjustment to the injury, or an exacerbation of premorbid psychiatric history. In particular, symptoms of anxiety and depression are commonly reported following brain injury. The following sections outline the manner in which anxiety and depression can manifest post-brain injury and how these factors can complicate recovery.

Anxiety, as a factor in brain injury, merits a comprehensive discussion due to its significance in complicating recovery. A recent comprehensive review of multivariable prognostic models for brain injury suggested that the most robust predictors in the multivariate models were preinjury mental health, acute postinjury neuropsychological functioning, early postinjury anxiety, and female sex.[38] In a comprehensive review article, Mallya and colleagues[39] reported that anxiety is one of the most frequently occurring psychiatric changes post-brain injury with prevalence rates ranging up to 70%. Moreover, the risk of postinjury anxiety is increased for those with a preexisting history of anxiety. Therefore, patients who sustain a brain injury and have a premorbid history of anxiety should be targeted for early cognitive-behavioral intervention. Additionally, it has been documented that the strongest concurrent indicators of PCS following a brain injury were anxiety and older age.[40] Kay and colleagues[36] detailed how psychological factors can accumulate and contribute to the symptom presentation after brain injury. For instance, compromised cognition following brain injury can result in significant frustration, psychological distress, social isolation, and alteration in self-image. As a result, patients may develop anxiety, followed by avoidance of anxiety-provoking situations. As psychological distress escalates, patients are likely to experience greater cognitive compromise, which then exacerbates their mood disturbance, creating a greater degree of functional disability than the injury itself. In light of these factors, managing anxiety symptoms in vulnerable individuals may be important to minimize prolonged symptoms. Providing education to patients about anxiety as a risk factor and incorporating cognitive-behavioral-based interventions, such as cognitive restructuring, diaphragmatic breathing, progressive muscle relaxation, mindfulness, biofeedback, and medication, for those with severe anxiety can significantly improve functional abilities and enhance other aspects of the rehabilitation process.

Although any degree of anxiety following TBI can be disruptive to daily functioning, some individuals may develop posttraumatic stress disorder (PTSD) related to the

mechanism of injury. Patients with PTSD should be evaluated and referred for treatment by mental health providers with specialized expertise. Although there has been some controversy regarding whether patients with more severe injury who are amnestic for the traumatic details of their injury meet criteria for PTSD, previous research found that such individuals had an elevated startle response, avoidance of stimuli similar to the trauma scenario, and increased irritability.[41] Thus, even individuals who are unable to recall the trauma causing their injuries may benefit from psychotherapeutic intervention to reduce their level of physiological arousal and desensitize them to stimuli associated with their injury.

Depression is also commonly associated with varying levels of brain injury severity. Some patients might experience depression initially, and for others, depression evolves over time as they are not able to return to their previous level of functioning and/or become frustrated by their progress in rehabilitation. In patients who are also engaged in litigation or seeking compensation, depression is one of the variables most strongly associated with poor outcome.[42] In a study of patients with mild TBI who were enrolled in an emergency department, depression was associated with PCS at 1 month and at 1 year, and PCS at 1 month was associated with continued PCS at 1 year.[43] In a study of patients with mild-to-moderate TBI, self-reported cognitive concerns were associated with major depression although controlling for depression did not completely eliminate all subjective cognitive concerns.[44] Depression has also been associated with regional atrophy in the left rostral anterior cingulate and bilateral orbitofrontal cortex in a study that examined degree of atrophy and depression symptoms in patients who sustained a TBI, primarily in motor vehicle collisions.[45] Given that damage to fronto-limbic-subcortical structures is common in TBI, depression is a frequent consequence across all severity levels of TBI.[46] Although a full discussion is beyond the scope of this chapter, there are multiple neuropsychiatric comorbidities associated with TBI in addition to anxiety and depression. For a review, see the article by Zgaljardic and colleagues[47] that describes post-TBI impulsivity, aggression, psychosis, and other personality changes and maladaptive behaviors. In a study of patients 10–20 years after sustaining a severe TBI, psychological factors, such as depression and anxiety, were more strongly associated with continued challenges in social and vocational functioning than cognitive deficits.[48] These results indicate that, even years after injury, depression can have a significant detrimental impact on functional ability and less than optimal adjustment to disability. Neuropsychological evaluation can be instrumental in identifying psychological factors affecting cognitive concerns and functional ability and in making recommendations for further evaluation and treatment. The impact of psychological factors on recovery and adjustment to injury cannot be overstated and should be a primary focus of clinical intervention.

PAIN

Many individuals who sustain a brain injury also experience comorbid orthopedic problems, tissue damage, and/or headaches. Evaluating pain is a crucial step in treatment planning as problems with chronic pain can lead to disruptions in daily functioning. Prior research has also found objective neuropsychological impairments related to chronic pain although there is conflicting information in the literature.[49] Although pain following brain injury can be experienced anywhere in the body, a frequent occurrence involves development of posttraumatic headaches (PTH). In one large cohort study, there was a 40% incidence rate of PTH at any given point during the first year post–brain injury with a cumulative incidence rate reaching 71% of the population studied.[50] Consistent with prior research, this study also found that premorbid headache is related to development of PTH following brain injury. From a neurocognitive perspective, chronic pain has been shown to place a person at risk for perceived cognitive impairment, particularly if there is the presence of comorbid depression.[51] Regardless, it is clear that individuals with chronic pain report cognitive concerns, which may lead to a prolonged recovery of cognitive symptoms following brain injury. As such, referral to a pain management clinic may be advantageous for patients with chronic pain issues. Further, initiation of group or individual therapy targeting pain management and distress tolerance may also be beneficial.

SLEEP

Adequate sleep is essential in promoting physical, cognitive, and psychological well–being. Sleep is frequently disrupted following brain injury secondary to various acute and chronic factors. For instance, many individuals report hypersomnolence during the acute recovery phase due to the brain's healing process. However, when sleep disturbance becomes chronic, it can have a negative impact on various aspects of daily functioning. It is important to note that brain injury can exacerbate existing sleep issues or possibly trigger a new onset of sleep disruption. In fact, incidence rates of reported sleep disturbance following a brain injury can be quite high, ranging anywhere from 30% to 70% based on prior research.[52] Sleep disruption can range from mild to severe and usually involves difficulty with sleep initiation and/or maintenance. There are various types of sleep disorders, such as narcolepsy, obstructive sleep apnea, sleep behavior disorders (e.g., sleep walking, night terrors), and insomnia. Although many people report general fatigue following brain injury, sometimes sleep disturbance can reach the level of insomnia.

From a neurocognitive perspective, insomnia can have various negative consequences, such as disruption in daily cognitive processes. For instance, many people describe feeling "foggy" or report slow information processing in the context of fatigue. Fortier-Brochu and colleagues[53] found worse cognitive outcomes (small-to-moderate in magnitude) in individuals with insomnia when compared to

healthy controls. In particular, reduced cognitive functions were noted in the domains of episodic memory, working memory, aspects of attention (i.e., reaction time, information processing), and problem solving.[53] If sleep problems persist, evaluation by a specialist is recommended in order to develop an appropriate treatment plan targeting sleep hygiene and possible consideration of acute intervention with medication management.

ALCOHOL AND SUBSTANCE ABUSE

Alcohol and substance abuse has been associated with poor medical, neurobehavioral, vocational, and life satisfaction outcomes following brain injury.[54–56] There are several important reasons why clinicians must consider and assess alcohol and substance use disorders in patients with brain injury. For example, due to reduced inhibitory control resultant from brain injury, individuals may then be predisposed to developing alcohol and substance use disorders and/or an exacerbation of their prior substance use. In addition, post-brain injury pain may lead to misuse of prescription medications, increasing the likelihood of developing a substance use disorder. As such, clinicians should attempt to avoid prescribing chronic narcotic and benzodiazepines (for pain and/or emotional symptoms) to these individuals for the abovementioned reasons.

One of the most highly abused substances for those with brain injury, is alcohol, as it has been estimated that approximately 40% of brain injury rehabilitation patients have a history of heavy alcohol use that preceded their injury.[54,57–59] In addition, studies have indicated that between 10% and 20% of individuals with brain injury develop an illicit substance use disorder postinjury (in addition to a large number of individuals with a substance use disorder preinjury who return to substance use postinjury).[57,60] Studies using quantitative neuroimaging have found greater nonspecific atrophy in brain injury patients with a history of alcohol/substance use when compared to nonusers,[54,61–63] possibly suggestive of the additive impact substance use has on brain injury. Although some research has indicated that acute alcohol intoxication may have a neuroprotective role following brain injury with regard to mortality,[64–66] other research has demonstrated that individuals who are intoxicated at the time of injury tend to have poorer cognitive recovery than those who were not intoxicated. Specifically, deficits in these individuals include impaired visuospatial ability and immediate and delayed memory, processing speed, and executive functioning.[67–70] However, acute alcohol intoxication may not be the primary contributory factor to poor cognitive outcome following brain injury as these individuals are also more likely to have a long-standing history of chronic alcohol use predating the injury.[69,71,72] Therefore, poor cognitive outcomes may reflect, or at least be exacerbated by, the deleterious effects of preinjury chronic alcohol use.

In summary, pre- and postinjury alcohol and substance use is negatively associated with different aspects of cognitive functioning following brain injury. As such, research regarding the effectiveness of current substance abuse treatments for individuals with brain injury should be a high priority with an understanding that treatments and services may need to be adapted to accommodate disability arising from TBI.

Computerized versus traditional testing

Computerized neuropsychological assessment devices (CNADs) have been increasing in popularity across several environments (clinical practice, including rehabilitation settings, research, and clinical trials). There are several positive attributes of CNADs, which include the capacity to test a large number of individuals quickly, the ability to precisely measure performance on time-sensitive tasks (e.g., reaction time), reduced time and costs, easily exported automated data, and increased accessibility when professional neuropsychological services are scarce.[73] Pre- and postinjury comparisons can also be made with some populations, such as athletes for whom preseason baseline data is available, which is also a benefit as individual changes can then be assessed. A drawback of computerized testing for very mild concussions is that they may lack sufficient sensitivity. For instance, research has shown that these instruments are sensitive in identifying clinical impairment within 24 hours of injury but do not add significant value over symptom assessment later.[74] This is not entirely unexpected given the rapid clinical recovery course from many sports concussions and the reduced sensitivity of relatively brief computerized testing, subsequently limiting the ability of these tests to detect subtle cognitive symptoms outside a narrow postinjury window. This supports the notion for more comprehensive, traditional (i.e., "pen and paper") neuropsychological evaluations so that a thorough assessment of individuals' functioning using a multimodal approach (e.g., visual, auditory, written, etc.) can be utilized. Moreover, this more comprehensive neuropsychological evaluation can be especially beneficial when recovery is protracted and/or atypical. Within a rehabilitation setting, CNADS can be used to track recovery and neurocognitive gains that can help target additional rehabilitation interventions and implementation of compensatory strategies.

Treatment

Rehabilitation is a critical step in recovery for individuals with acquired brain injury. Physical and occupational therapy are obvious treatment staples immediately following moderate-to-severe brain injury as motor and functional disturbance are common. However, even with good physical recovery, persisting cognitive dysfunction can be debilitating and is a significant cause of disability after brain injury.[75,76] Further, problems with returning to preinjury routines and activities can be associated with reduced perceived self-efficacy, leading to worse quality of life outcomes.[77] Various rehabilitation strategies have been developed to address both initial and persisting cognitive concerns following a mild-to-severe acquired brain injury.

In particular, cognitive rehabilitation (CR) is an intervention aimed at promoting implementation of compensatory strategies to address areas of cognitive dysfunction while also training previously learned skills to promote recovery in those areas. A comprehensive review conducted by Cicerone and colleagues found that CR training was shown to have greater benefit than conventional methods of rehabilitation compared to no active treatment, indicating CR is the best course of treatment for individuals post-acquired brain injury.[78] There is further evidence to suggest CR therapy can offer improvements (small-to-moderate effect size) in attention following brain injury.[79] Generally speaking, it is advantageous to initiate CR as early as feasibly possible in the recovery process. This is especially the case given that the greatest cognitive gains are typically made 12 months postinjury with additional improvements seen up to 24 months. Various clinical providers may be skilled in implementing CR therapy, including occupational therapists, speech and language therapists, neuropsychologists, and some mental health providers. The two primary modes of CR therapy include computerized and traditional CR, and the following sections outline each in greater depth.

TRADITIONAL REHABILITATION TRAINING

During traditional CR training, the patient typically works one-on-one with a therapist to regain cognitive skills that were negatively impacted by the brain injury and/or to put compensatory strategies in place to address cognitive difficulties that may remain stable. The neuropsychological evaluation can be very helpful in informing this treatment process, particularly when considering the degree of expected improvement in cognitive abilities following brain injury. Exercises used during traditional CR training may include paper and pencil tasks targeting various aspects of cognition, especially attention, memory, processing speed, and executive functioning. As previously mentioned, traditional CR training can be completed by working one-on-one with a therapist and sometimes in a group format. Advantages of individual CR training include the development of an individualized therapy plan and the ability to provide direct attention during the session. However, there are also benefits to group CR training, such as the support received from peers and also the facilitation of social interaction skills.

COMPUTERIZED CR TRAINING

Computer-based CR integrates digital technology to target common cognitive concerns following brain injury, such as disruptions in attention, working memory, processing speed, problem solving, and memory. Computerized CR programs involve a range of exercises using digital software to train and relearn various cognitive skills. Advantages to using computerized CR methods include development of a personalized training program based on baseline testing, recovery tracking through objective data, and access to immediate feedback on performance. In addition, some computerized CR programs can be self-administered at home, which can reduce health care-associated costs and also increase accessibility of treatment for many individuals.

COMPARISON OF TRADITIONAL AND COMPUTERIZED REHAB TRAINING

The literature shows variable results regarding the efficacy of both computerized and traditional CR training following acquired brain injury. A comprehensive review conducted by Rees and colleagues[80] revealed that approaching CR differently depending on the functional difficulties and stage of recovery can be advantageous to patients.[80] Recommendations for specific CR strategies based on the acuity and mechanism of brain injury have been outlined by Cicerone and colleagues (2002) in order to promote optimal recovery. For instance, the use of external aids (e.g., planner, calendar) and/or internal strategies (e.g., imagery) can help individuals compensate for commonly reported memory concerns, and initiating attention training during postacute rehabilitation may be advantageous following acquired brain injury.[81] A systematic review conducted by Bogdanova and colleagues[82] revealed generally positive findings regarding cognitive improvement following computerized CR, particularly in the domains of executive functioning and attention. Although these results are promising, the review of existing literature raised concerns and limitations regarding the use of computerized CR rehabilitation in general. For instance, methodological problems in some of the prior research cause concern regarding generalizability of results. In addition, there is a lack of standardized procedures used across different computerized CR programs, which leads to challenges with research design and measuring objective outcomes. For example, a popular "brain training" program was recently fined by the FTC for making false and exaggerated claims about the benefits of their program in improving functional abilities and preventing or delaying cognitive decline.[83]

In sum, the literature suggests that both traditional and computerized CR methods may benefit patients following acquired brain injury at least to some degree. It will be important to address each therapy option with the patient during treatment planning. In particular, consideration should be given to the patient's ability to access care, such as barriers to transportation, financial limitations, and level of caregiver support. Evaluating needs on a case-by-case basis will be most advantageous in selecting the most appropriate course of treatment (e.g., computerized vs. traditional CR) when making referrals.

NEUROPSYCHOLOGICAL REFERRALS

When to make the referral

Neuropsychological assessment can be very helpful in identifying, assessing, and elucidating not only the cognitive deficits experienced by patients with brain injury, but also in assessing those abovementioned factors, including psychological and emotional distress (e.g., anxiety and depression),

physical problems (e.g., pain, sleep dysfunction), and psychosocial stressors, all of which may be contributing to the patient's functional disability. Having a complete picture of these issues is particularly important in rehabilitation settings so that each factor can be targeted in treatment to optimize recovery. In addition, neuropsychological evaluations are of critical importance for both the referring provider and patient, answering diagnostic and treatment-related questions. Diagnosis typically occurs in the rehabilitation setting; therefore, the role of the neuropsychologist is less for diagnostic purposes and more focused on how the resulting cognitive and behavioral deficits following brain injury will affect current and future daily functioning.[84,85] Typical referral questions can generally be divided into several categories, including diagnosis, characterizing neuropsychological status, treatment planning, determining the efficacy of treatment, tracking recovery, and for forensic purposes (e.g., litigation). Referral questions can also be used for clinical research purposes, such as determining the effects of certain medications compared to others.[84,85] As such, due to a broad range of possible questions, when making a referral for neuropsychological evaluation, providers should be as specific and direct in specifying the referral question(s). It is also crucial to provide the neuropsychologist with all relevant medical records and pertinent information, such as the date of injury, acute medical care (including Glasgow Coma Score if available), patient's current and resolved symptoms, onset and time course of these symptoms, and previously conducted evaluations or procedures (e.g., prior neuropsychological testing, brain imaging, EEG, etc.). The neuropsychologist should also be informed if there is a medico-legal component of the evaluation and/or if there are any other components (e.g., return to play, learn, work, drive, etc.) that are under consideration at the time of the neuropsychological evaluation.

Deconstructing the report

The neuropsychological evaluation will typically evaluate and assess several functional cognitive domains, including attention/concentration, processing speed, executive functioning, language/speech, visuospatial/construction, learning and memory, sensory/motor as well as emotional and personality functioning. In addition, neuropsychological evaluations frequently incorporate an assessment or estimate of an individual's intellectual functioning (verbal and nonverbal) and may include academic skills and abilities (reading, writing, arithmetic). The specific battery of neuropsychological tests is typically determined at the discretion of the neuropsychologist and is based on the referral question, medical records, and information obtained during the clinical interview with the patient and, if possible, collateral report. Another major factor contributing to test selection is the severity and extent of the patient's injury (e.g. moderate-to-severe brain injury vs. mild brain injury) as this will likely impact the individual's capacity to complete the chosen tasks. In addition, other factors, including fatigue, pain, and premorbid intellectual functioning, are also critical for the neuropsychologist to keep under consideration to assess the individual's level of functioning and abilities. The battery will be subsequently modified accordingly based on these factors, further emphasizing the importance of specific and direct referral questions, in order to obtain the most direct and efficient plan to assess, evaluate, and answer these questions.

It should also be noted that a clinical neuropsychological evaluation is distinguished from abbreviated screening assessments of cognitive function (e.g., MMSE, MOCA) due to the implementation of several standardized psychometric tests with well-established normative data, which can be adjusted for the individual's age, ethnicity, and education to achieve the best comparison to demographically similar individuals. Although the use of normative data provides the neuropsychologist with a comparison group to gauge the individual's relative performance, repeated neuropsychological evaluations are very beneficial in assessing for interval change and also assist in evaluating treatment effectiveness and whether treatment modifications are warranted.

Although neuropsychological reports vary by provider with respect to length, format, and extent of included background information, there are several critical pieces of necessary information. The neuropsychological report contains various standard elements, including specifics of the evaluation, such as dates of evaluation, name and credentials of staff involved in the evaluation as well as the referring provider, sources of information (e.g., medical records, patient interview, collateral interviews, etc.), description of procedures and tests administered, and psychometric information (normative data and diagnostic classifications). The report should also include the presenting concerns of both the patient and referring provider and also detail relevant background information, including medical, psychiatric, educational, and social history. Any relevant behavioral observations should also be contained within the report. Perhaps the most important, and certainly the most relevant, sections of the report include the results, summary, impressions, and recommendations. The results can be provided in a variety of formats (e.g., table, narrative, or a combination of both). The summary and impressions should generally not be limited to describing the neuropsychological scores of the patient or simply a description of the patient's cognitive strengths and weaknesses. Rather, this section should specifically note if there is evidence of brain dysfunction and the degree of the individual's impairment and relate this to the patient's current level of functioning and predicted future functioning. It is, therefore, critical to tailor the neuropsychologist's recommendations to the individual's cognitive and emotional functioning as well as to his or her access to resources to optimize follow-through with the recommendations. Finally, any applicable diagnoses resultant from evaluation should be clearly stated with the rationale and justification for the diagnoses clearly stated in the summary and impressions section as well.

Neuropsychological recommendations

Neuropsychological recommendations typically include compensatory strategies for addressing any observed and/or perceived difficulties by the patient, referral for additional diagnostic procedures (e.g., imaging), and referral for behavioral or psychiatric intervention based on the emotional sequelae either resulting from or exacerbated by the injury. In terms of rehabilitation, there have been three established levels of focus for these recommendations. The first level is to remediate any underlying impairments, which is typically accomplished by the repetitive and frequent training and practicing of cognitively focused techniques to maximize the individual's improvement. After this stage is complete, the second level involves improving functional outcomes by providing modifications based on the individual's current level of functioning, usually through the utilization of the compensatory strategies mentioned above. The third level involves providing recommendations for assisting the individual in managing his or her subjective experiences and instruction in coping and effectively processing the changes in cognitive functioning (e.g., through therapy, counseling, etc.). By addressing these three levels through implementation of cognitive training, modifying daily routine based on the current level of functioning, and assisting the individual with coping emotionally with functional changes, we hope the potential for a successful outcome can be increased.[86]

Suggestions on providing feedback to the patient

The findings of the neuropsychological evaluation, including the conclusions, impressions, and recommendations, should be provided to both the referring provider and to the patient. Due to the length and complexity of a neuropsychological evaluation and report, a feedback session should be conducted with the patient, preferably via an in-person conversation, during which an open discussion can take place and the patient's questions can be directly addressed. Although the impressions and recommendations should be clearly stated in the report, this feedback session should provide clarity to the findings and confirm the patient's understanding of the findings. Moreover, this will give the neuropsychologist the opportunity to present the findings in laymen's terms as opposed to the medical terminology likely used in the report. The relative strengths and weaknesses should be reviewed with the patient, and compensatory strategies to offset any weaknesses should be provided and discussed during this session. Any recommended additional referrals (e.g., medication management via a physician, psychotherapy, rehabilitation, further diagnostic work-up) should be elaborated upon with the patient during this feedback session.

The feedback process also gives the neuropsychologist the opportunity to provide education to the individual as well as the individual's support system regarding what to expect with regard to treatment outcomes to ensure appropriate understanding.[87] At this point, information can be provided regarding typical symptoms after brain injury, and individual factors that can complicate recovery should be targeted for therapeutic intervention. For example, providing education about the important role of attention as the input into memory is often very enlightening for patients. When it is explained that disrupted attention prevents information from being fully encoded and, thus, not stored in memory and education is provided to patients regarding the many factors that can interfere with attention, patients are likely to feel an improved sense of control and efficacy in improving their attention and, thus, the gateway to other cognitive abilities.

Information for caregivers

As described in the previous sections, brain injuries often involve multifactorial medical, cognitive, and emotional/behavioral concerns, which must be addressed in treatment. Given the complexity of these injuries, providing psycho-education on the expected symptoms, outcomes, and recommendations for recovery is crucial to facilitate the patient's understanding of the diagnosis and treatment. However, it is equally important to provide psycho-education on brain injury to caregivers because their role in the patient's recovery process can be substantial. If the patient is amenable and provides the appropriate consent, it is often beneficial to include the caregiver in medical appointments, treatment planning meetings, or feedback sessions. From a neuropsychological perspective, involving the caregiver when explaining cognitive testing results can be especially advantageous. For instance, the patient may have cognitive impairments that limit his or her ability to fully comprehend the significant amount of information provided during a neuropsychological feedback session. Further, the patient may require functional assistance from a caregiver to implement any recommendations and compensatory strategies discussed during feedback. Even beyond psycho-education, keeping the caregiver apprised of expected treatment outcomes and avenues for respite care, if needed, may help to combat issues such as caregiver burnout. In addition, helping the family understand the patient's challenges can facilitate understanding and empathy as well as provide suggestions for practical support.

CONCLUSION

In summary, the neuropsychological evaluation can provide a framework for understanding the patient's current functional abilities and can be used to inform and guide rehabilitation interventions. As detailed earlier, given the range of injury severity in TBI and the many individual factors that can affect functioning, neuropsychological assessment is helpful in assessing premorbid abilities, cognitive strengths

and weaknesses, and comorbid factors. The identification of complicating comorbidities, such as psychological distress, pain, insomnia, and/or substance abuse history, can guide additional interventions. Targeting treatment of these complicating factors can significantly improve recovery of function and quality of life. Neuropsychological evaluation can be very instructive in identifying each patient's unique cognitive profile, which can be used to provide individualized rehabilitation treatment and to track recovery of function.

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Neuropsychological interventions following traumatic brain injury

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INTRODUCTION

Traumatic brain injury (TBI) can result in myriad physical, cognitive, and emotional impairments that disrupt an individual's capacity to live independently, perform social and occupational roles successfully, and maintain preinjury quality of life.[1] For most individuals, resolution of symptoms following a single uncomplicated mild TBI (e.g., headache, fatigue, poor concentration, etc.) generally occurs within hours to weeks, but sequelae of moderate or severe TBI often persist for the remainder of the person's life. As a result, many individuals with TBI have a relatively high rate of neuropsychological symptoms even several years postinjury, including cognitive dysfunction and emotional distress.[2–4] A number of rehabilitation interventions have been developed to address cognitive and emotional sequelae of TBI to promote independent living and facilitate community reintegration.[5] Broadly, these interventions are aimed at improving the individual's ability to effectively perform cognitive tasks, cope with psychological distress, and increase self-awareness and self-efficacy.

The purpose of this chapter is to provide an overview of neuropsychological rehabilitation; briefly review the research demonstrating its efficacy; identify recurrent and often unresolved themes in the relevant literature; present an overview of empirically based neuropsychological interventions for cognition, emotion, and self-awareness; and discuss future directions of neuropsychological rehabilitation for TBI.

NEUROPSYCHOLOGICAL REHABILITATION

Neuropsychological rehabilitation refers to a broad range of interventions, including cognitive rehabilitation, psychotherapy, psycho-education, and vocational training, ideally with some involvement of family members or significant others in the treatment process.[6] Studies involving neuropsychological rehabilitation began appearing in the literature in the late 1970s and early 1980s and, in a relatively short period of time, have contributed greatly to the rehabilitation of individuals with TBI.[7] The interventions described in this literature lead to functional improvement and increased engagement in productive and meaningful activities in several areas, including social and community participation and employment. Since the emergence of the first comprehensive and coordinated efforts to address impairments resulting from TBI more than 40 years ago, neuropsychological rehabilitation has spurred significant research interest. This interest grew from the need to identify

interventions that led to demonstrable improvement in individuals' real-world functioning.[8]

Neuropsychological rehabilitation interventions are applicable to individuals who are at all stages of brain injury recovery, i.e., acute, subacute, and postacute.[9] Soon after injury, neuropsychological interventions consist mainly of cognitive interventions to improve fundamental cognitive functions, such as orientation and simple attention. In addition, neurobehavioral approaches are used to manage emotional and behavioral symptoms, such as agitation.[4] In the subacute and postacute stages, the scope of interventions increases to address a range of basic and more complex cognitive and neurobehavioral symptoms, such as executive dysfunction, anxiety, and depression.[9] Of note, however, is that the literature to date has not demonstrated increased benefit associated with early intervention, nor has a postinjury "critical period," during which treatment is more likely to be effective, been identified. In other words, it is never too late to begin treatment.

Principles of neuropsychological rehabilitation

Prigatano[6] developed a set of guidelines for the practice of neuropsychological rehabilitation meant to enhance the patient's therapeutic experience and maximize benefit from treatment. He delineated 13 principles that encompass neuropsychological rehabilitation and address, among other issues, the importance of understanding the individual's subjective experience of his or her injury, the interaction of premorbid cognitive and personality characteristics with presenting symptoms, impairments in self-awareness and the need to address these in treatment, the inclusion of retraining and management of cognitive deficits, psychotherapy and coping skill-building for emotional distress, and support for families and staff to regulate their own emotional responses during the rehabilitation process. In addition, Prigatano underscored the dynamic nature of neuropsychological rehabilitation, which is fluid and constantly informed and transformed by scientific efforts and phenomenological approaches as well as the clinical judgment of the therapist.

From isolation to integration: The evolution of comprehensive treatment

The range of interventions that constitutes neuropsychological rehabilitation for TBI has evolved over time.[6] At the core of neuropsychological treatment is cognitive rehabilitation. Frequently used interchangeably with the term *cognitive remediation*,[7] cognitive rehabilitation was originally conceptualized as a group of interventions designed to equip TBI survivors with skills and strategies that would enable them to complete tasks that would otherwise be extraordinarily challenging or impossible because of injury-related impairments. As cognitive remediation interventions proliferated, the treatment needs of individuals with TBI were better understood, and evidence for the additional benefits of milieu treatment for TBI-related deficits became available.[9–11] These interventions began to be administered in concert with other interventions, such as psychotherapy or instruction in the use of assistive technology.[7,12] Cognitive remediation that only targeted discrete cognitive skills in isolation (e.g., attention), although effective at improving these skills,[8,11] did not reliably result in improved daily functioning or quality of life whereas such improvements were more often observed following treatment in holistic or comprehensive cognitive programs.[13–15] Therefore, Sohlberg and Mateer[16] suggested replacing the term *cognitive remediation* with *cognitive rehabilitation* and defined the intervention as "rehabilitation of individuals with cognitive impairments" (p. 3)[16] to capture the breadth of TBI survivors' treatment needs, which extends beyond retraining and managing cognitive difficulties to include management of affective and behavioral symptoms and ultimately improved psychosocial functioning and community reintegration.

In the mid-1970s, treatment programs were developed that combined complementary interventions in order to yield improvement in both gross cognitive skills and real-world functional abilities.[10] Yehuda Ben-Yishay was the first to develop a comprehensive holistic day treatment program for individuals with brain injury that incorporated a combination of individual and group treatment approaches as well as community activities. This innovative, comprehensive intervention received rapid recognition, was adapted to a variety of treatment settings, and has become viewed as the standard of care in cognitive or neuropsychological rehabilitation.[6] The defining characteristics of a comprehensive holistic day treatment program include neuropsychological interventions to improve cognitive skills, increase individuals' awareness of deficits, and address interpersonal, social, and emotional concerns in individual and group sessions; a transdisciplinary treatment approach with clearly defined and regularly monitored treatment goals; opportunities for involvement of significant others; independent living and/or vocational trials; and assessment of outcomes.[9]

Is there evidence that cognitive rehabilitation works?

Theoretical and conceptual developments; technological advances in neuroimaging, measurement, and treatment applications; clinical observations; and significant improvements in research methodology have resulted in the accumulation of knowledge and evidence that have made possible the evaluation of cognitive rehabilitation and other neuropsychological interventions.

The toolkit of cognitive rehabilitation interventions has grown rapidly in the last four decades. Interventions to improve visual-perceptual skills,[17] language,[18–20] attention,[21–23] memory,[24–27] and executive functioning following TBI have been developed.[28–30] As these interventions grew in number, so too did the need to empirically validate their effectiveness as most of these interventions were developed in treatment settings based on clinical observations and not through controlled research trials. Responsiveness to the

research need resulted in accumulation of evidence supporting the clinical effectiveness of cognitive rehabilitation, heightened awareness of the need for methodological rigor in studies of TBI rehabilitation interventions, and identification of treatment-related issues that require further investigation, such as the interaction between demographic, injury, and treatment variables on outcome.

The current evidence base supports the efficacy of cognitive rehabilitation interventions. As early as the late 1970s, research findings supported the effectiveness of these interventions for improving cognitive functioning.[7,8] More recently, three systematic reviews of the cognitive rehabilitation literature were conducted by the Cognitive Rehabilitation Task Force of the Brain Injury–Interdisciplinary Special Interest Group of the American Congress of Rehabilitation Medicine and were published in 2000, 2004, and 2011.[8,11,31] These reviews evaluated the literature on cognitive rehabilitation interventions for TBI and stroke. The conclusions based on these reviews were that 1) cognitive rehabilitation was effective over traditional types of treatment in 80% to more than 90% of studies, 2) studies that showed no advantage were comparing one cognitive rehabilitation treatment with another, and 3) in no study was cognitive rehabilitation less effective than alternative treatment. Interestingly, the Cicerone et al. 2000[8] review, which spanned almost 25 years of research, yielded 171 studies (29 of which were Class I), and the 2004[11] review, which spanned 5 years, included 87 studies (17 of which were Class I). The 2011 review[31] also spanned 5 years and included 112 studies, 14 of which were Class I. The relatively larger per year yield illustrates both the field's responsiveness to the need for evidence on treatment efficacy and improvements in methodological rigor of studies over time. Nevertheless, Cicerone et al.[11] caution that the quest for evidence should now shift from validating the effectiveness of cognitive rehabilitation treatments to better understanding the more nuanced aspects of treatment, such as those patient characteristics that maximize benefit from treatment.

Recurrent themes in neuropsychological rehabilitation

In reviewing the descriptive and empirical literature on clinical interventions, certain themes become evident and generally pertain to different trends and unresolved issues in the field. Three of these issues are discussed in the following section: 1) the apparent dichotomy between restorative and compensatory interventions; 2) the selection of appropriate outcome measures; and 3) the timing of the intervention.

The apparent dichotomy between restorative and compensatory interventions

Cognitive rehabilitation interventions are commonly classified as either restorative or compensatory. The goal of restorative approaches is to strengthen or return to baseline a particular cognitive function through training and repeated use of that particular function. Restorative interventions include practice drills and repetitive exercises.[16,32,33] For example, a restorative approach to the remediation of sustained attention would be an exercise during which the individual is asked to listen to a long series of numbers and respond only when he or she hears a specified target number. The goal of compensatory approaches is to improve one's ability to complete specific real-world tasks as independently as possible without attempting to strengthen the underlying cognitive processes required for the task.[33] Compensatory approaches circumvent the dysfunctional cognitive process through the use of external aids, such as checklists with step-by-step procedures on how to accomplish a task or a notebook to record important information that might otherwise be forgotten.

Many have raised concerns about the value of restorative approaches in cognitive remediation as evidence has failed to show significant improvement in cognitive functioning following intensive practice and/or exercise involving the affected cognitive process.[33] However, research in the area of interventions for hemiparesis following brain injury has demonstrated the value of restorative approaches. Specifically, constraint-induced movement therapy (CIMT) has been shown to result in gains in upper extremity motor function.[34–37] CIMT involves restraining the unaffected limb to compel the individual to use the paretic limb. The resultant improvement in motor function in the paretic limb is thought to be subserved by cortical reorganization. In addition, it is thought that CIMT prevents the recruitment of compensatory mechanisms that would favor increasing functionality of the unaffected limb and facilitate "learned nonuse" of the affected limb.[38] Given that CIMT has shown positive results even in those with remote injuries, Hart[33] observed that the CIMT literature challenges the belief that spontaneous recovery of a cognitive function is only possible within a certain time interval following injury, after which no further improvement is attainable without the application of compensatory mechanisms.

Of note is that the use of compensatory strategies leads to behavioral changes, which could, in turn, lead to functional and structural changes in the brain, blurring the distinction between compensation and restoration. In an innovative study using CIMT, Gauthier et al.[39] observed not only functional improvement in motor ability in a sample of stroke patients, but also increases in gray matter volume in sensorimotor cortex and the hippocampus, suggesting neuroplastic changes both within and outside of neural structures directly involved in movement. A critical conclusion to be drawn from this study[39] is that behavioral changes (in this case, use of a paretic limb) can indeed lead to structural changes in the brain. This causal relationship calls into question the classification of neuropsychological interventions as either restorative or compensatory. This distinction might be at best unhelpful and at worst arbitrary and impractical. Effective neuropsychological interventions result in learning

and behavioral changes that enable individuals to function more successfully in their daily lives. Learning any skill is likely to be associated with neurobiological change on a structural and functional level.

Methodologically rigorous studies examining this association as it pertains to cognitive rehabilitation are needed, but the fact that "compensatory" interventions often result in "restoration" of functional skills is clear nonetheless.

The selection of appropriate outcome measures

Neuropsychological rehabilitation is multifaceted with diverse interventions and multiple treatment goals, making it challenging to determine how to appropriately assess the impact of treatment and to identify the level at which (cognitive, emotional, behavioral, functional) changes have occurred. Ultimately, the goal of rehabilitation is to improve an individual's ability to function independently in the community. Accomplishing this requires addressing emotional issues arising from injury-related losses (e.g., physical or functional impairments, social role changes, etc.) and the emotional response to emerging awareness of the potential impact of the injury. Treatment also focuses on regaining functional independence, which can hinge on one's ability for self-care, to the ability to support self and others financially, and to participate in meaningful and productive activities, such as gainful employment, recreation, volunteering, and education. Given the diversity and complexity of these goals, how can it be demonstrated that neuropsychological interventions lead to positive changes?

Traditionally, the neuropsychological rehabilitation of individuals with TBI was focused on improving functioning in specific cognitive domains, e.g., memory, attention, executive functioning, etc. Measures were selected to assess specific neurocognitive functions in each of the domains being treated. The effectiveness of such isolated cognitive interventions is typically assessed by measuring 1) performance on the specific task for which instruction was provided, 2) performance on everyday tasks that require the cognitive skills on which treatment has focused, and/or 3) changes in day-to-day function and participation in community activities.[40] Measuring outcome by comparing an individual's performance on a task that is identical or similar to the task that was used during training is particularly relevant to determining whether the skill being trained has been learned. However, a more important question is how does specific skill training improve the person's ability to function in "real life?" For example, a study involving individuals with severe memory and executive functioning impairments investigated their ability to learn a stepwise procedure for using email by counting the number of correct procedural steps achieved when attempting to send an email.[24] After training was completed, participants were able to use the original and a slightly altered version of the email interface successfully, but their performance on a computer memory game did not improve, suggesting minimal generalization of the skills learned in treatment to a different task requiring similar skills and knowledge. Frequently, neuropsychological measures are often used to evaluate effectiveness. For example, the effectiveness of interventions to improve attention might include measures such as the Digit Span subtest of the Wechsler Adult Intelligence Scale, the Paced Auditory Serial Addition Test (PASAT), Verbal Paired Associates from the Wechsler Memory Scale, Auditory Consonant Trigrams, Trail Making Test, and the Continuous Performance Task (e.g., Cicerone,[21] Middleton et al.,[41] Park et al.,[42] Sohlberg et al.,[23] Serino et al.[22]).

However, the extent to which performance on neuropsychological measures is associated with competence in specific day-to-day activities is unclear. Performance on many neuropsychological tests represents an index of cognitive dysfunction, and predicting how that measured dysfunction will translate into functional impairments in daily activities is difficult, especially when tasks or activities are overlearned, assisted by others, and/or can be performed imperfectly without obvious consequences. In addition, more complex aspects of behavior might not be adequately measured by neuropsychological tests. Therefore, changes in performance are often assessed via self-report questionnaires, such as the Attention Rating and Monitoring Scale (ARMS) to assess improvement in individuals' attention complaints,[21] the Dysexecutive Questionnaire (DEX) or Frontal Systems Behavior Scale (FrSBe) to assess problems with behavior or activities heavily reliant on executive functioning, and the Beck Depression Inventory to assess depression. The validity of self-report questionnaires in individuals with TBI may be weakened by injury-related cognitive impairments (e.g., not remembering pertinent information or endorsing depression symptoms, such as indecision or inability to concentrate, that are more likely due to neurological injury) as well as by lack of awareness of the deficits (anosognosia, e.g., not being cognizant of frequent lapses in attention during a conversation). Therefore, the validity of self-report measures when applied to individuals with TBI is dependent on interpretation by a clinician capable of disentangling neurological and psychological contributions to individuals' self-report.

Nevertheless, as Cicerone and colleagues[11,31] highlight in their reviews of the cognitive rehabilitation literature, interventions resulting in improvement on neuropsychological tests and self-report measures of daily functioning often do not result in improving the individual's daily functioning as well. Cicerone et al.'s review strongly supports the notion that neuropsychological tests frequently used as outcome measures might not adequately capture treatment-related reductions in psychosocial functioning and overall level of disability. In fact, research regarding the relationship between neuropsychological test scores and functional outcome is inconclusive with some studies supporting the relationship between the two domains of function (e.g., Cicerone et al.,[5] Ownsworth & McFarland,[43] Thickpenny-Davis & Barker-Collo[44]) and other studies showing no relationship between neuropsychological test scores and

functional improvement (e.g., Klonoff et al.,[13] Malec & Basford,[9] Mills et al.,[14] Teasdale et al.[15]). For example, Rattok et al.[45] found that including cognitive remediation in group treatment for individuals with TBI resulted in some advantages in performance on neuropsychological tests but did not result in behavioral, interpersonal, or vocational functioning gains. In their review of rehabilitation interventions for memory deficits, Quemada et al.[46] found no relationship between performance on memory tests and ability to carry out activities of daily living. Similarly, there was no relationship found between performance on tests of memory and family reports of the affected individuals' memory failures in daily life. In a recent, randomized, control trial evaluating the efficacy of the Short-Term Executive Plus (STEP) cognitive rehabilitation program to improve executive functioning following TBI, Cantor et al.[47] found no pre- to posttreatment improvement on individual measures of executive functioning, but did find significant improvements in a composite score comprised of multiple measures of executive functioning as well as improvements in self-reported executive function as assessed by the FrSBe and self-reported problem solving as assessed by the Problem Solving Inventory (PSI).

A trend exists among milieu-oriented programs to employ measures other than neuropsychological tests to evaluate treatment effectiveness and to assess meaningful changes in individuals' ability to function successfully in daily life. A majority of studies investigating the effects of comprehensive-holistic day treatment programs have incorporated functional measures in their outcome assessment procedures. For instance, several programs have used the Community Integration Questionnaire, a 15-item questionnaire that assesses home integration, social integration, and productive activities (e.g., Cicerone et al.,[5] Goranson et al.,[48] High et al.,[49] Seale et al.[50]) to measure the frequency of participation in activities following TBI. Ability, adjustment, and participation have frequently been measured with the Mayo-Portland Adaptability Inventory (Constantinidou et al.,[51] Harradine et al.,[52] Malec,[53] Malec & DiGiorgio[54]). Other functional indices have included independence in personal and domestic activities of daily living,[55] staff ratings or work readiness/eagerness,[13] emotional and psychosocial adjustment,[56] adaptation to community skills, self-care, involvement with others, regulation of affect, performance on vocational trials,[45] and return to and longevity of productive activities, including gainful employment and enrollment in school or other training programs.[13,57,58] Incorporating functional measures in intervention research is critical because the ultimate goal of any intervention is to improve function in real-life settings.

A related issue is that of skill transfer and generalizability.[59] Skill transfer occurs when an individual takes a skill he or she has learned for the purpose of carrying out one task and uses that skill to complete a completely different task. For example, independent grocery shopping might be a treatment goal, and making a shopping list after taking careful inventory of one's pantry might be the means to achieve that goal. In this scenario, skill transfer would have occurred when the individual is able to inventory his or her closet, make a list of clothing items needed for the upcoming winter, and independently shop for the needed clothing. However, these skills might not generalize to other activities, such as preparing a meal or paying bills. Generalization refers to the ability to use and apply a learned strategy to a broad array of novel situations. Consistent with the goals of rehabilitation, the skills learned during treatment are expected to be applied outside of treatment. In order to measure an individual's mastery of skills they have been taught in treatment, one must measure that individual's ability to use those skills in practical ways. Therefore, functional measures likely measure generalization of learning to real-life situations to a greater extent than do neuropsychological measures.

The timing of the intervention

The overall positive effects of cognitive rehabilitation treatment for individuals with TBI have been clearly established,[8,11] and several physiological factors have been identified as underlying those effects.[60] What has not been clearly addressed in the literature is whether there is a critical period during which neuropsychological interventions are more effective and are more likely to produce gains, especially in the postacute stage. Many studies have included individuals with relatively recent injuries because these individuals are more easily recruited, probably due to their active involvement in a rehabilitation system of care. Conclusions of studies using samples of individuals who are less than 6 to 12 months postinjury, however, may be confounded by the effects of spontaneous recovery.[60] It is often assumed that the effects of rehabilitation are weakened unless interventions are administered soon after injury. The first year after injury is usually considered the most critical in terms of neurological recovery, after which the rate of neurological recovery is expected to plateau.[61] This information is often presented to patients and their families without further qualification, and it is often met with a sense of haste, urgency, and/or pessimism, creating a belief that improvement will be limited if treatment is not received within this "critical" window. However, this assumption is not strongly supported by the available data. Some studies find early rehabilitation more beneficial.[62–65] For instance, Malec[62] reported more positive vocational outcomes for individuals beginning treatment within a year postinjury compared to those who began later. Nevertheless, in this study, both groups benefitted from treatment, suggesting that effective interventions are beneficial at any time postinjury. Other studies comparing early and late initiation of neuropsychological rehabilitation treatment have shown no differences in psychosocial outcome,[61,66] independence and community integration,[49] or performance on neuropsychological tests.[67] The lack of strong and conclusive evidence and the persistent need for further research in this area notwithstanding, there is no critical window for new learning to take place. Learning can occur at any point postinjury

and learning has no end point. Therefore, we do not know when a person can no longer continue to improve. It follows that intervention can begin at any point postinjury and with no time-dependent limit on the degree to which an individual can benefit from treatment. It is critical for clinicians and individuals with TBI to understand that appropriate interventions could lead to improvements in cognitive, emotional, and psychosocial functioning regardless of the length of time since injury.

NEUROPSYCHOLOGICAL INTERVENTIONS: SOME HIGHLIGHTS

The following sections briefly describe evidence-based neuropsychological interventions for improving cognition, emotional functioning, and awareness of deficits following TBI found in the literature. In addition to those studies referenced, the reader is directed to the Cognitive Rehabilitation Manual authored by the Brain Injury-Interdisciplinary Special Interest Group of the American Congress of Rehabilitation,[68] which describes in detail neuropsychological interventions shown to result in positive functional gains in methodologically rigorous outcome studies.

Interventions for cognition

ATTENTION

Interventions for attention deficits vary as a function of the particular attention component or system they target. For example, several interventions have been developed to improve working memory and range from simple tasks, such as using flash cards to improve orientation,[69] to more complex tasks, such as mental arithmetic, anagram solutions, and n-back procedures and other serial logic verbal tasks.[21,22,70]

One of the most commonly used interventions for improving attention has been developed by Sohlberg and Mateer.[71] Their Attention Process Training program, now in its third iteration (APT-III), consists of a variety of visual and auditory tasks organized hierarchically in terms of difficulty and designed to remediate putatively different components of attention (focused, selective, sustained, divided, alternating; see Ashley et al.[60] and the ACRM Cognitive Rehabilitation Manual[68] for more information). APT-II expanded on its predecessor by incorporating more complex and intensive tasks to address less severe attention deficits often observed in more mild injuries, and APT-III added attention exercises using visual stimuli and exercises patients could perform independently outside of a treatment session to further facilitate skill training.

APT has demonstrated efficacy for improving attention skills in a number of studies, is easy to implement clinically, and is designed to facilitate skill generalization to individuals' daily activities.[71,72] In order to accomplish generalization, the authors have incorporated "generalization tasks" into the interventions that are hierarchically implemented and monitored. Treatment is typically conducted in individual sessions with feedback on performance provided to the patient consistently throughout the session. The ease of using APT notwithstanding, the role of a trained clinician in treatment using the training is indispensable as only a clinician can select those interventions most relevant to the individual patient's treatment needs and goals while maximizing skill generalization.[31] The clinician is also critical to helping the patient identify and remediate ineffective cognitive approaches to the task.

MEMORY

Memory deficits interfere significantly with a person's ability to function independently and can interfere with treatment by impairing the patient's ability to learn and/or recall the content of treatment sessions. Improvements in other cognitive domains may be further hampered because of difficulties in learning and recalling new material, difficulties remembering when and how to use rehabilitation tools and strategies, and difficulty maintaining motivation in both the patient and the clinician due to the extensive time and effort required to notice improvements.[73] Deficits in attention might also contribute to memory dysfunction by negatively impacting an individual's ability to learn, or "encode," the content of treatment sessions. This illustrates the point that some cognitive abilities, particularly attention, are foundational in that they support more complex cognitive abilities, such as learning. Treatment must first focus on the most foundational skills that have been impaired in order to improve more complex skills as training more complex skills when foundational skills are impaired will yield little improvement in more complex skills.[68,74]

Both restorative and compensatory approaches have been used in treating memory deficits. Restorative approaches have included word-list learning, paragraph listening, visual imagery, and use of mnemonic strategies,[32,68,75] all of which are especially useful for mild memory deficits.[31] Compensatory tools seem to be more effective for improving daily function than is training designed to improve memory processes directly,[76,77] and they include memory notebooks, calendars/date books, and other paper-and-pencil methods of recording and tracking information in addition to technology-based tools, such as voice recorders and note-taking, calendar, and alarm/reminder applications run on personal computers, smartphones, and tablets.[78–82] Technology-based tools have the advantage of increased portability, functionality, and accessibility as compared to paper-based tools, but training patients to effectively use these tools can be problematic if the patient has severe cognitive deficits and/or limited experience with technology.[68,82]

Undoubtedly, the most widely used and researched compensatory tool for memory rehabilitation is the memory book, and it is one of the most effective tools in memory rehabilitation. Sohlberg and Mateer[75] presented a method of training individuals to develop and use a

structured memory book that is personally relevant to the individual. In determining the contents of the memory book, the authors suggested reviewing the person's living and work environment as well as current and anticipated level of cognitive functioning. The memory book can include sections for orientation, a memory log, a calendar, "things to do," transportation, a "feelings log," and "important information." Their method for memory book training consists of three phases: acquisition, which involves introducing and increasing the individual's familiarity with the sections and purpose of the notebook; application, which refers to training the individual to use the memory book by simulating real-world circumstances in the treatment session; and adaptation, which involves reviewing and refining the individual's use of the book in naturalistic settings with the goal of skill transfer. Using the pioneering work of Sohlberg and Mateer[75] as a springboard, Donaghy and Williams[73] developed a protocol for memory book training to assist clinicians working with individuals with memory deficits to increase the effective use of the memory book by their clients. Effective use of a memory notebook should include the ability to schedule future events (prospective memory) and track past events, a note-keeping system that makes retrieval effortless, and ease of use that fosters independence.[68,73,75] Teaching patients to effectively process, break down, and record information is vital to successful acquisition of memory book skills.

Despite substantial evidence for the effectiveness of the memory book in addressing memory deficits,[81,83–86] inconsistent use of the book by patients is a recurrent problem that reduces benefit. McKerracher[87] identified several barriers to successful use of memory books and other external memory aids, including lack of awareness of memory deficits, reluctance to use strategies that might draw others' attention to the individual's deficits, perceiving use of aid as "cheating," concern that aids will reduce the chance of natural recovery, and/or severity of memory impairment and other cognitive problems (e.g., executive impairments). In addition, family or other individuals might have low expectations for the individual's independence and not reinforce use of memory aids. These factors illustrate the need for psychotherapeutic and/or family interventions as complements to memory book training. Finally, evidence suggests that patients often require extensive training and reinforcement to use external memory aids effectively and consistently,[88] highlighting the need for clinicians to remain undeterred in their efforts to teach and reinforce the use of external memory aids despite resistance, reluctance, and/or confusion from patients who are otherwise good candidates for training.

Prospective memory

Prospective memory refers to the ability to remember to carry out a certain action at a specified time in the future or in response to a specific future event.[89] This is vital to maintaining successful performance in work, social, and daily living situations, but prospective memory failures tend to outnumber retrospective memory failures (inability to recall previous actions or information) in individuals with TBI.[89] Consequently, considerable efforts have been made in the last decade to develop cognitive rehabilitation interventions to enhance prospective memory. Einstein and McDaniel[90] identify two components to prospective memory: 1) remembering what actions are to be carried out and the cue for implementing the action and 2) recall and initiation of the action at a given time following the cue. Prospective memory has been enhanced significantly with the use of technology-based tools, such as smartphones, which can be programmed to provide portable cues and reminders that are visual and/or audible, but challenges, such as training individuals to use the technology and ensuring consistent use, remain.[20,28,78–80,91,92]

EXECUTIVE FUNCTION

"Executive functioning" refers to a broad range of abilities that subserve goal-directed behavior, including initiation, planning, organization, and monitoring of self and the environment.[11] Additional executive functions have included anticipation, action sequencing, cognitive flexibility,[93] problem solving,[94–96] and regulation of emotion and behavior.[33] Executive dysfunction has a significant impact on emotional, behavioral, and social outcomes following brain injury.[16,94] Consequently, the treatment of executive dysfunction has received significant attention in the literature. Interventions have been based on explicit theoretical models of executive function (e.g., D'Zurilla & Goldfried,[97] Luria,[95] Shallice & Burgess[98]); comprehensive-holistic day treatment programs that emphasize cognitive operations, such as self-awareness and daily problem-solving;[5,13,53,94,99,100] and specific interventions focused on improving problem solving,[94,101–103] goal management,[29] and self-regulation.[94,101,104]

Treatment of executive dysfunction generally involves teaching individuals to use metacognitive strategies[94,101,105,106] to consciously regulate their own cognitive process, e.g., learning how to learn and/or how one learns best, and using that knowledge to improve information processing. The key to improving executive functioning by mastering metacognitive skills is increasing self-awareness. This awareness allows one to formulate attainable and personally relevant goals and heighten the ability to self-monitor one's thought and action to assess performance, reduce or prevent errors, enhance self-control, and initiate action or behavioral change.[105] In a systematic review of the literature on executive functioning following TBI,[105] Kennedy et al. identified metacognitive strategy instruction as a common intervention among several studies, including randomized clinical trials (e.g., Rath et al.,[100] Levine et al.[29]). Similarly, Cicerone and colleagues have identified metacognitive strategy training as a practice standard in their most recent systematic review on the cognitive rehabilitation literature.[31] Metacognitive strategy instruction includes using and internalizing step-by-step procedures intended to enhance problem solving, planning, organization, and multitasking by increasing the capacity for self-regulation.[105]

Cantor et al.[47] have recently published data on the efficacy of a day treatment program to improve executive functioning following TBI (the Short-Term Executive Plus program, or STEP). STEP is comprised of group problem-solving and emotion-regulation skills training in concert with individualized APT and daily sessions devoted to generalizing skills learned in the program to the participant's individual needs and goals. The problem-solving intervention entails learning a step-by-step procedure that facilitates identification of problems, reduction of the problem to more elemental components, generation of possible solutions, carrying out one or more possible solutions, and self-monitoring the result.[94] The emotion-regulation intervention (described in more detail in the following section) is designed to heighten participants' awareness of triggers for emotional dysregulation and the thoughts, feelings, bodily sensations, and behaviors that result from the trigger. The intervention is also designed to teach participants ways to regulate these components of their emotional experience in order to reduce unpleasant or unproductive emotional states and formulate more productive, goal-directed behavior. Generalization of problem-solving and emotion-regulation skills to multiple settings is achieved by incorporating repetition and feedback throughout the treatment in both individual and group formats. The STEP program was found to result in significant improvement in executive functioning and problem-solving ability. There was no treatment effect on emotion-regulation ability, but many participants did not have significant emotion dysregulation at baseline, raising the possibility of reduced power to fully evaluate the potential benefits of the emotion-regulation component of the program.

Interventions for emotion

The consequences of TBI on emotions can be conceptualized in two broad categories: emotional symptoms arising from brain dysfunction and those arising from emotional/adjustment reactions to personal loss and disability. Emotional symptoms related directly to neural trauma have been associated with damage to the prefrontal cortex and limbic structures[107,108] and include affective disinhibition, emotional blunting, decreased initiative, emotional lability, aggression, agitation, misperception of emotional cues, and lack of empathy.[109–114] Excessive laughing or crying can be observed after TBI, but this can be due to pseudobulbar affect (PBA) when accompanied by involuntary emotional expressions in the absence of a corresponding subjective emotional state (e.g., crying when feeling emotionally content). PBA is a motor disorder attributable to pathological disinhibition of motor pathways involved in emotional expression and must be distinguished from a mood disorder for proper management.[115] Emotional symptoms that are reactions to the sequelae of the injury include clinical disorders characterized by depression, anxiety, or posttraumatic stress and adjustment reactions, including feelings of grief and loss, low self-esteem, social isolation, loneliness, agitation, and suicidal thoughts.[3,111,116]

Interventions for neurologically based emotional symptoms include metacognitive strategies to increase emotional self-regulation and prevent impulsive or damaging behaviors[94,101,117] as well as training in emotion recognition and correct interpretation of emotional cues.[109,118] These interventions have yielded promising results with respect to the management of emotion perception and regulation.

Several psychological interventions have been adapted to address emotional/adjustment reactions to TBI sequelae. Cognitive behavioral therapy (CBT) has been used extensively as a first line treatment for depression,[119] posttraumatic stress disorder,[120–122] anxiety,[123,124] irritability and aggression,[125] and anger[104] after TBI. It is often helpful to adapt CBT treatment protocols for individuals with TBI by incorporating principles of cognitive remediation to address cognitive factors that can impede treatment success,[126,127] such as deficits in attention, memory, and/or executive function. Tsaousides and colleagues[47,82] have developed an emotion-regulation skills intervention (EmReg) based on principles of CBT and mindfulness-based therapy that involves teaching individuals to identify the primary components of an emotional experience, including emotional triggers, bodily sensations, thoughts, emotions, and behaviors, and to use self-managed interventions to address distress manifested in these different areas. For example, CBT techniques, such as cognitive reappraisal and evidence-gathering, are used to address distressing thoughts, and relaxation techniques can be used to address bodily sensations, such as shortness of breath or muscle tension. The components of the emotional experience are conceptualized as being interrelated, so applying an intervention in one area (e.g., thoughts) can improve an individual's experience in another area (e.g., bodily sensations) with the ultimate goal being regulation of emotion sufficient to allow for good problem solving and self-monitoring, and the selection of productive, goal-directed behavior. EmReg incorporates elements of cognitive remediation in its emphasis on developing better metacognitive awareness of emotional experiences, self-monitoring the behavioral results of these experiences, and generation of possible alternative behaviors with the use of problem solving.

Other models of psychotherapy introduced as potential interventions for individuals with TBI include Orlinsky and Howard's Generic Model of Psychotherapy as applied by Coetzer.[128] The Generic Model is based on nonspecific factors of psychotherapy, such as the rapport between therapist and patient, to elicit therapeutic change. In addition, a recent study by Ashman et al.[129] found that both CBT and supportive psychotherapy were effective in treating post-TBI depression. In order to accommodate the cognitive challenges of individuals with TBI, the format of the CBT was altered to include components of cognitive rehabilitation; for example, additional sessions were added to allow for repetition of complex material.

Interventions for self-awareness

Decreased awareness of TBI-related deficits can be the result of neurologically based anosognosia and/or psychogenic denial.[6,130,131] Regardless of etiology, the treatment of poor awareness of deficits is vital to the success of cognitive rehabilitation because a clinician generally cannot effectively treat a symptom the patient does not notice. Consistent with this, diminished self-awareness has been associated with poor rehabilitation outcome.[6,130,131] In contrast, increasing awareness of deficits can result in psychological distress. Several models exist that explain impaired self-awareness due to TBI. Crosson et al.[132] introduced the pyramid model of awareness, which distinguishes between intellectual awareness (the ability to understand that there are certain deficits in functioning), emergent awareness (the ability to recognize a functional problem when it occurs), and anticipatory awareness (the ability to predict that an area of deficit may lead to problems in functioning). Other models include Langer and Padrone's[133] tripartite model of unawareness: unawareness of information, unawareness of implications, and psychological denial; Fleming and Ownsworth's[130] model of awareness of objective knowledge: awareness of the functional implications of deficits for daily activities and the ability to set realistic goals; and Allen and Ruff's[56] model, which includes the ability to attend to, encode, and retrieve information about the self, the ability to compare current and premorbid functioning, and willingness to report self-perception to another person. Finally, Giacino and Cicerone[134] identified three sources for limited awareness: cognitive impairment (especially attention, memory, and self-monitoring), psychogenic denial, and failure of higher-order cognitive systems to recognize deficits and incorporate them in self-knowledge. In addition to the neurocognitive and psychological sources of unawareness typically described in these models, Fleming and Ownsworth[130] identified social-environmental factors that contribute to diminished awareness. These factors include minimal opportunities to obtain information or to observe deficits in a social context, reluctance to disclose information about the deficits due to concerns about how the information will be used, and the interference of cultural values with the neuropsychological rehabilitation process.

Neuropsychological interventions to treat self-awareness deficits include milieu-oriented treatment programs aimed at increasing awareness via peer, staff, and family feedback; psycho-education and psychotherapy;[6,130,135,136] and cognitive remediation interventions, such as therapist monitoring of task performance and generating lists of strengths and weaknesses.[137] These interventions are based on the idea that unawareness of deficits can have both a neurological and psychological origin (e.g., as the result of a defensive coping style).[6,138] In a randomized clinical trial to improve executive function described in a previous section,[94] the investigators have observed significant improvements in self-awareness. Although anecdotal, the investigators attribute the observed improvement to comprehensive treatment involving both individual and group sessions emphasizing metacognitive training with the group sessions allowing participants to observe deficits in others and share challenges (e.g., "what he is saying has also happened to me").

Psychotherapeutic interventions for lack of awareness of deficits are aimed at exploring the meaning of loss following TBI and ameliorating the effects by developing meaningful and realistic goals. Langer and Padrone's[133] tripartite model of unawareness provides a useful framework for developing psychotherapeutic interventions to raise awareness. Within this model, interventions to increase awareness of deficits include psycho-education and feedback about the individual's TBI-related impairments. Interventions to increase awareness of the implications include building a supportive structure to allow the individual to learn compensatory strategies and avoid failures. Interventions to address the psychological denial include assessing the client's readiness to recognize deficits and to strengthen their tolerance for resulting distress. Interventions based on Crosson et al.'s[132] pyramid model have included psycho-education, feedback, planned failures, and emotional support to increase intellectual awareness, feedback during and after task completion to increase emergent awareness, and helping the individual create plans and anticipate problems to raise anticipatory awareness. Self-determination[139] is an approach based on the pyramid model that includes education, practice in safe and structured environments, and application in real-life situations.

Other interventions to increase self-awareness have included structured experiences, direct feedback, support groups, and a game format. Structured experiences are preplanned and personalized exercises to increase awareness, metacognitive knowledge, and self-efficacy. Techniques including anticipation of obstacles, self-prediction, self-checking, self-questioning and self-evaluation, time-monitoring, and role-reversal are used in the duration of the structured experience. Direct feedback involves the therapist's commentary on the individual's task performance. Direct feedback is beneficial when it is specific, timely, consistent, and respectful and when the unawareness is neurological rather than psychogenic. Finally, support groups and games that provide education about brain injury and its sequelae can be used to improve awareness in a nonconfrontational manner, but the impact of these experiences on individuals' self-appraisal ability is inconsistent.[130,140]

FUTURE DIRECTIONS IN NEUROPSYCHOLOGICAL REHABILITATION

Technology and neuropsychological rehabilitation

Technological aids have been employed in the treatment of individuals with cognitive deficits since the early days of cognitive rehabilitation. Use of computers to project visual and verbal stimuli to provide training in attention, memory,

processing speed, and problem solving has become commonplace over the past decade. Over time, technology in neuropsychological rehabilitation has progressed from the use of computers as passive tools to facilitate cognitive training to active training tools that could expand the scope of training as well as compensatory tools or cognitive orthotics[12] that could be used in everyday settings to support functioning and reduce disability. Examples of technology as training tools include the use of computers in the training of memory,[141–143] attention,[141,144] problem solving,[141] and job simulation.[145] The advantage of using technology as a training tool is that it permits the administration of tasks that would otherwise be impossible to administer. However, computer-assisted training is generally not associated with better outcomes than is therapist-assisted training.[31,141,144]

The use of technology to develop compensatory tools has resulted in the creation of devices that can enable completion of tasks heavily reliant on complex cognitive processes[78–81] and, at the same time, result in significant improvements in psychosocial functioning,[146] rendering the individual with TBI more competent in task completion, time management, and record keeping, while bolstering his or her self-efficacy. Lopresti[12] provides an extensive review of existing technological aids, which he divides into technologies for memory and executive function impairments and technologies for information processing impairments. Devices for memory and executive function range from digital watches and alarms to more sophisticated devices, such as voice organizers (some of which will replay a message aloud at a prespecified time); mobile phone-computer interactive systems; and handheld devices, such as personal digital assistants. Devices for information processing impairments include use of a keyboard for typing instead of writing, software that alters the features of computer text (e.g., size, color) to increase reading ease, and speech output/speech recognition software.

An additional use of technology includes teletherapy. Bell et al.[147] tested the effectiveness of telephone interviews on behavioral outcomes. The content of the phone call was a mixture of counseling, motivational interviewing, and psycho-education. Their results showed significant improvement in functional measures in those participants who received telephone counseling compared to those who did not, suggesting that telephone counseling may be an effective, low-cost, and easily accessible alternative intervention. Melton and Bourgeois[148] assessed the effectiveness of a learning and memory intervention over the telephone and identified three advantages: 1) increased generalization as the skill is being learned in the individuals' everyday environment, 2) increased accessibility to individuals with TBI who might be otherwise unable to receive treatment due to practical barriers (e.g., limited transportation, financial constraints, mobility issues, living a distance from treatment providers), and 3) the potential to reduce absenteeism. Similarly, Tsaousides and colleagues conducted a pilot study[82] to determine the feasibility of delivering an emotion-regulation skills intervention in a group format to TBI survivors via videoconferencing and found excellent ease of use, attendance, and self-reported satisfaction and adequate skill acquisition among participants. The feasibility of delivering this intervention via videoconferencing is currently being studied in a large-scale study, including participants with TBIs of varying severities from around the United States and abroad. Study enrollment is limited to those with clinically significant emotional dysregulation at baseline, and more extensive data on efficacy is being collected. Data from this study should be available in early 2017.

Given consumer satisfaction with the use of technological devices[149] and the encouraging results from small-scale studies, it is expected that in the next few years several improvements and adjustments will be made to create portable electronic devices that will further facilitate daily functioning in those with TBI. The pervasiveness of technology in all aspects of daily living suggests that a shift from paper-and-pencil to electronic compensatory tools is imminent. This transition might be met with resistance, especially from older individuals and those less familiar with technology, highlighting the need for the field to develop effective methods of introducing technology to the uninitiated. Use of technological aids may allow individuals to use compensatory tools more consistently and make these tools more attractive, especially to younger individuals who might be reluctant to use tools that might identify them to others as having injury-related deficits.

Although the use of technology in TBI rehabilitation is expected to increase in the next few years, technological aids should not be intended to replace a therapist but rather to enhance the effectiveness of treatment. Findings from studies showing no advantage of computer-assisted interventions over traditional interventions[141,144] illustrate the importance of the clinician as an active participant in the treatment. Therapists set and maintain the structure of treatment, determine treatment needs and readiness, provide feedback and guidance, and teach and reinforce the use of compensatory methods. Therapists also help the patient process emotional reactions that might otherwise impede daily functioning or progress in rehabilitation, and they facilitate the inclusion of family or other collaterals in the treatment, which is often helpful in reinforcing the use of rehabilitation strategies in daily life and maximizing functional gains.[73,78–81] Most importantly, a positive working alliance between therapist and client facilitates treatment and contributes to successful treatment outcome.[6,150,151]

CONCLUSION

Neuropsychological rehabilitation is continually evolving in both principle and practice due to a growing body of research with ever-increasing methodological rigor, but a grand unifying theory has yet to be developed. Similarly, a "one size fits all" treatment approach will likely remain elusive and perhaps rightfully so. Each cognitive rehabilitation patient presents with a unique combination of injury-related deficits, premorbid strengths and weaknesses, life goals, and personal values and beliefs. Therefore, clinicians

must stay current with the literature on available interventions, evidence for efficacy, and outcomes as a function of patient characteristics and must flexibly apply interventions with an understanding of the individual needs and goals of the patient.

Ylvisaker[152] points out that there has been a paradigm shift from more traditional approaches, the goal of which is to "fix" the cognitive problem, to more contextualized approaches whose goal is to enable individuals to live a fuller life by reducing the burden caused by the cognitive problems. Wilson[153] stated that

> We have moved on from the early days of cognitive rehabilitation with its emphasis on drills and exercises to try to reduce basic impairments, to a more individualized approach addressing the everyday manifestations of these impairments, i.e., disabilities and handicaps…Cognitive rehabilitation should focus on real-life, functional problems, it should address associated problems such as mood and behavioral problems in addition to the cognitive difficulties and it should involve the person with the brain injury, relatives and others in the planning and implementation of cognitive rehabilitation. (pp. 98–99)

Finding a balance between these two conceptualizations of cognitive rehabilitation continues to present a challenge, and this challenge underlies the controversies of outcome measurement, distinction between domain-specific training and generalization, and the apparent contrast between restoration and compensation. Yet, these controversies continue to stimulate new innovations by clinicians and researchers, whose work constitutes a quest to find better ways to help TBI survivors improve their cognitive and emotional functioning in order to regain their independence.

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The use of applied behavior analysis in traumatic brain injury rehabilitation

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INTRODUCTION

The issue of maladaptive behavior, as an associated consequence of traumatic brain injury (TBI), is one of the most important aspects in brain injury rehabilitation because behavior disorders, often, represent a significant barrier to effective rehabilitation and functional outcome.[1–6] Changes in personality and behavior are also familiar consequences of TBI.[7–15] In the acute stages of recovery from TBI, it is common for a person to exhibit a variety of behavior disorders.[16,17] Such behavioral disturbances are considered by many to be a phase of normal recovery of cognition.[18,19] When these behaviors continue beyond acute recovery, however, and begin to form standard patterns of interaction with others,

genuine concern is warranted.[20] Behavioral disorders are disturbing to families and staff,[21,22] disruptive to therapy,[23,24] and costly,[25,26] and they can lead to criminality,[27–31] negatively impact future quality of life,[32] and jeopardize patient safety;[33] thus, effective behavior analysis can be a powerful tool for teaching people more positive ways of interacting with their environment.

The purpose of this chapter is to clearly illustrate and simplify the concepts, techniques, and uses of applied behavior analysis with those suffering from TBI. Although it is assumed that the reader has some basic understanding and/or experience with applied behavior analysis, difficult technical terms have been avoided whenever possible. When only technical jargon will suffice to effectively explain or label a particular concept or method, the term is defined.

In keeping with the more practical nature of this chapter, a couple of areas related to applied behavior analysis will not be covered. First, single-subject research design will not be discussed. Although single-subject research is important to the scientific advancement of applied behavior analysis, we feel that it requires special attention that is beyond the scope of this chapter. Second, there will be no instruction for measuring inter-rater reliability. Substantiating agreement between independent observers is important in determining reliability of data, like single-subject research design, but it falls within the boundaries of research and not necessarily the practical application of behavior technology.

Included in this chapter are the tools necessary to organize and carry out effective behavior programming for people with TBI. The person with TBI represents a special challenge to rehabilitation professionals and family members. Maladaptive behavior is only one facet of a complex neurobehavioral picture. Cognitive, physical, and emotional changes resulting from brain injury must be taken into consideration in the overall behavioral treatment of the patient with TBI. Behavioral treatment does not work alone. Behavioral programming is most effective when it is integrated with a comprehensive rehabilitation program. For example, as a patient's information processing skills increase, so does the ability to deal with cognitively challenging situations. As adjustment to disability improves, the patient becomes better equipped to face the loss of functional ability. As motor and perceptual skills develop, so does the opportunity to live more independently. Behavior programs provide a "meta-structure" within which various therapeutic disciplines are carried out.

The challenge is to rehabilitate people with TBI in the least restrictive setting possible.[34] We hope this chapter will provide therapists, educators, family members, and other involved people with the materials and methods necessary to help patients with TBI regain their highest level of independence.

THE BRAIN–BEHAVIOR RELATIONSHIP

As many readers know, TBI can have numerous serious consequences. Physical, cognitive–communicative, functional, and psychological skills can be severely affected. Common areas of physical deficit are ambulation, balance and coordination, fine motor skills, strength, vision,[35,36] and endurance.[37,38] Cognitive deficits can encompass language and communication, information processing, memory, and perceptual skills.[39–41] Functional skills, such as hygiene and grooming, dressing, and money management, are usually affected, to name a few.[42] A person's psychological status is also stressed. Depression, anxiety, adjustment to disability, and sexuality issues are frequently encountered by people with TBI.[43–54] Any or all of these difficulties may bear directly on the behavior of a patient. Recent studies have even linked cognitive recovery with the degree of psychopathology.[19,55] Compound these with medical issues, such as location of damage, severity of injury, seizure disorders, and sleep disturbance,[56] as well as preinjury characteristics of personality,[37–60] intelligence,[61,62] cognitive reserve,[63,64] substance abuse,[65,66] and learning style, and a complex neurobehavioral picture is created.

Brain injury can occur in a number of ways. TBIs, as opposed to stroke, Alzheimer's, Parkinson's, etc., typically result from accidents in which the head strikes an object (e.g., windshield, ground). This is the most common type of TBI. However, other acquired brain injuries, such as those caused by insufficient oxygen (e.g., cardiac arrest, near drowning, suffocation),[67] poisoning (e.g., toxic fumes, chemicals), electrical shock, or infection (e.g., encephalitis, malaria), can cause similar deficits.[68–70] Many of the most severely behaviorally challenged patients we have worked with over the years were injured in these "less common" ways.

Mild TBI (MTBI), another important category of brain injury, is characterized by one or more of the following symptoms: a brief loss of consciousness, loss of memory immediately before or after the injury, any alteration in mental state at the time of the accident, or focal neurological deficits.[71,72] In many MTBI cases, the person is only "dazed," yet continues to endure chronic functional, cognitive, and motor difficulties.[73–76] Some people suffer long-term effects known as postconcussive syndrome (PCS).[77–80] Persons suffering from PCS can experience subtle, yet significant, changes in cognition[81] and personality[82–84] and even experience seizure-like symptoms.[85]

All of these brain injuries will influence behavior. The relationship between the brain and behavior is very complex and beyond the scope of this chapter to comprehensively review; however, it is important for those involved in behavioral programming to have at least a rudimentary understanding of this association because of its significant, underlying effect on behavior.[86] Problems such as denial, apathy, irritability, emotional lability, impulsivity, frustration, intolerance, lack of insight, inflexibility, perseveration, confabulation, lack of initiation, poor judgment and reasoning, and decreased social skills can often be linked to specific areas of brain damage.[87–94]

To begin with, most TBIs result in widespread damage to the brain. This is because the brain is "bounced" and

"twisted" inside the skull during the impact of an accident. Nerve cells are torn from one another in what is known as diffuse axonal injury.[95–99] Localized damage also occurs when the brain is forced against the skull during the "acceleration–deceleration" phase of an accident. The brain stem, limbic system, frontal lobe, and temporal lobes are particularly vulnerable in this type of injury.

The brain stem is located at the base of the brain near bony areas. Aside from regulating basic arousal and vegetative functions, the brain stem is involved in attention and, thus, short-term memory skills. Deficits to these areas can lead to disorientation, frustration, and anger. The limbic system, higher up in the brain, is associated with emotions and affect.[100] Disorders of the limbic system can result in explosive rage.[101–104] Connected to the limbic system are the temporal lobes, which are involved in many cognitive skills, such as memory, language, and sequencing. Damage to the temporal lobes or seizures in this region have been associated with a number of behavioral disorders.[105,106] A part of the anterior temporal lobes, the amygdala, has been implicated in social behavior. Lesions in this area have been associated with increased fear and anxiety and may contribute to a number of social disorders.[107,108] The frontal lobes are almost always injured due to their size (taking up 29% of total cortical space) and their location near the front of the cranium.[109] The frontal lobes, like the temporal lobes, are involved in many cognitive functions. They are also considered our emotional control center and home of the personality.[110–112] Damage to these areas, resulting in what is, sometimes, called frontal lobe syndrome, can result in decreased judgment and increased impulsivity, irritability, social impairment, and aggression.[113–118] Neuroendocrine damage after TBI is receiving increasing attention because of its potential effect on recovery, function, and behavior. Consequent hormone deficiencies can directly influence the brain and result in fatigue, depression, fear, and stress.[119–121]

MEDICATION

It is now widely recognized that pharmacological intervention for behavioral disorders with the postacute patient with TBI is not necessarily the treatment of choice.[122–124] It is much more desirable to implement behavior programs that manipulate the environment and help the patient develop self-control.[125–127] Many medications used in the past with other populations to combat behavior problems may elicit more agitation from traumatically brain-injured persons or confuse them at a time when attention and arousal are often already problematic.[128–131] Recent studies have indicated that disorientation, which can be compounded by medications, is closely related to both physical and verbal aggression with the traumatically brain-injured.[132] Recent research has also indicated that the use of neuroleptics during the acute stages of recovery can have a negative impact on recovery of cognitive function.[133] Although a number of medications, such as haloperidol, amantadine, and propranolol, have proven useful in treating behavior problems in the early stages of recovery from TBI,[134–147] the brain-injured person may experience more cognitive confusion and react with increased agitation. The use of stimulants, such as methylphenidate, to reduce behavior problems has shown mixed results.[148–150] This is not to say that medications should never be used, but there should be careful monitoring of the interactive effects of medication with behavior as well as awareness of the potential for oversedation, increased seizure activity and health risks,[151,152] or chronic overuse resulting in permanent side effects for the patient, such as tardive dyskinesia, motor restlessness, and others.[153–155]

The treatment setting may be such that pharmacological management is necessary. In those unfortunate circumstances, medications should be closely monitored because they can often lose effectiveness.[156,157] The choice, then, may be between prescribing no medication, trial periods of alternative medications, or medication dosages to the point of sedation. Once a person has progressed beyond acute hospitalization, many behavior medications can be tapered while closely observing the person's behavior within the structure of a behavior program.[123] This approach makes it much easier to reach an educated decision regarding continuation of the medication.

ETHICS

Applied behavior analysis (sometimes referred to as behavior modification) has always been plagued by controversy. The mere mention of behavior modification is usually enough to elicit a strong response from professionals and the public alike. For many, the use of behavior modification principles and techniques is, in some way, "forcing" a person to change against his or her will. Deep-rooted concepts regarding democracy, free will, and humanism are threatened by the notion of applying scientific methods to change human behavior.

What many of us fail to realize is that our behavior is continuously being modified. Influences from politicians and parents to television and teachers help shape and pattern our behavior. Applying behavior analysis is not meant to assume an authoritarian position over a person but to analyze the relationship between events and behavior. The goal is to increase, not decrease, personal freedom by expanding the behavioral options available to the person, thereby enhancing opportunities for community, social, and family interaction. Such opportunities are severely restricted for people with behavior problems. Applied behavior analysis is a structured discipline for reducing behaviors that limit independence and increase behaviors that empower a person.

Of course, misuse of applied behavior analysis has occurred, and punishment techniques have been overused. However, the notion that applied behavior analysis should not be used or, more specifically, that punishment should be severely limited, is neither rational nor practical. The alternatives to applied behavior analysis are typically medication,[158] physical restraint,[159,160] or life in a locked

institution,[161] all of which carry their own ethical ramifications.[162] Applied behavior analysis, used within proper guidelines, is an effective and humane method for reducing maladaptive behaviors and teaching new skills.

Although a number of authors and governmental agencies have published guidelines for positive behavioral services and procedures, the Behavior Analyst Certification Board has established the "Professional and Ethical Compliance Code for Behavior Analysts"* that provides standards to which professionals should adhere. These codes provide guidelines for professionals in 10 areas, including responsibility conduct; responsibility to the client; assessing behavior; behavior change programs; and responsibility to the profession, colleagues, and research.[163]

The Association for Behavior Analysis International (ABAI) "Right to Effective Treatment" statement also provides the following guidelines[164]:

- *An individual has a right to a therapeutic environment*. A physical and social environment that is safe, humane, and responsive to individual needs is a necessary prerequisite for effective treatment.
- *An individual has a right to services whose overriding goal is personal welfare*. Both the immediate and long-term welfare of an individual are taken into account through active participation by the patient or an authorized proxy in making treatment-related decisions.
- *An individual has a right to treatment by a competent behavior analyst*. Professionals responsible for delivering, directing, or evaluating the effects of behavioral treatment possess appropriate education and experience.
- *An individual has a right to programs that teach functional skills*. The ultimate goal of all services is to increase the ability of individuals to function effectively in both their immediate environment and the larger society.
- *An individual has a right to behavioral assessment and ongoing evaluation*. Prior to the onset of treatment, individuals are entitled to a complete diagnostic evaluation to identify factors that contribute to the presence of a skill deficit or a behavioral disorder.
- *An individual has a right to the most effective treatment procedure available*. An individual is entitled to effective and scientifically validated treatment. In turn, behavior analysts have an obligation to use only those techniques that have been demonstrated by researchers to be effective, to acquaint consumers and the public with the advantages and disadvantages of these techniques, and to search for the most optimal means of changing behavior.

As the number of people with TBI increases, rehabilitation programs will face difficult ethical questions.[165] Accountability is the key. All facilities carrying out behavior programs should have clear goals; comprehensive data collection; and the ability to provide rationale for starting, continuing, and ending a behavior program. This includes a means of closely monitoring all the previously discussed guidelines to operate ethically sound behavior programs. Applied behavior analysis is a powerful tool for changing behavior. If used correctly, patients are given the opportunity to relearn many lost skills and to become as independent as possible in the shortest amount of time.

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GENERAL MANAGEMENT GUIDELINES

The environmental conditions posed by treatment and care settings for people with TBI can have significant impact on behavior. Organizing the therapeutic setting and carefully planning an approach to the patient can increase opportunities for successful learning and decrease the chances of a behavioral episode. The following are 10 recommendations for structuring a positive learning environment for the person with TBI:

- *Allow for rest time*. People with TBI, especially in the initial stages of recovery, can be extremely fatigued.[166–168] Monitor the person's behavior and schedule rest periods during those times related to an increased probability of problem behavior. A word of warning however: Do not forget to reduce these rest periods as the person recovers and gains endurance.
- *Keep the environment simple*. People with TBI are easily overstimulated by their surroundings. The inability to filter out external stimuli can lead to confusion and increase the chances of a behavioral episode. Interruptions and distractions should be kept to a minimum and the therapy session format kept consistent.
- *Keep instructions simple*. Instructions, prompts, and cues should be kept as concrete and simple as possible. This may mean writing down instructions as well as stating them. It may also mean keeping verbal prompts to a minimum. Many people with TBI have difficulty processing auditory information. Instead, try using nonverbal instruction techniques, such as modeling (demonstrating) or gesturing.
- *Give feedback and set goals*. Self-monitoring skills can be diminished with the traumatically brain-injured.[169–171] They must rely on others to provide feedback until the ability is relearned.[172–174] Provide frequent and consistent positive feedback of success. Most people respond well to supportive encouragement. Setting goals helps the patient predict where he or she is "going" with therapy and provides him or her with some incentive for completing therapeutic tasks.[175,176]
- *Be calm and redirect to tas*k. People who cannot control their own behavior need others to demonstrate and produce a stable, nonthreatening environment. Remaining calm while the patient is escalated can help reduce agitation and decrease the chances of

inadvertently reinforcing the patient with attention for acting out. A related method gaining widespread attention, "gentle teaching," uses a variation of this approach as a central technique.[177–179] It involves ignoring the exhibited behavior, redirecting the patient to the task,[180] and rewarding successful performance. However, gentle teaching's rather unstructured approach, lack of scientific support, and philosophical assumptions contrast sharply with traditional behavior analysis.[181]

- *Provide choices*. Research indicates that providing patients with choices can reduce serious behavior problems[182] and increase on-task behavior.[183] Giving them opportunities to choose tasks can be an effective technique when working with the traumatically brain-injured. It allows patients an element of freedom and a measure of control over their environment. Some patients, however, require "limited" choices that decrease the range of decisions so that they are not overwhelmed or left with an open-ended opportunity to say "no."
- *Decrease chance of failure*. Do not work above the patient's level of ability. This will only lead to frustration and increase the chance of a behavioral episode. Try to keep the success rate above 80%. This ensures that the patient is challenged while at the same time feeling successful. A variation of this technique is known as behavioral momentum. This procedure involves presenting tasks with which the patient is likely to comply immediately before presenting tasks that are likely to be more problematic.[184] This establishes a high rate of performance (and, we hope, reinforcement) just prior to more difficult tasks with the idea that compliance will be more likely to continue.
- *Vary activities*. Although there is a need for consistency and repetition when working with the person who is traumatically brain-injured, there is also a need to keep the session interesting. Therapy can become boring and frustrating if the same tasks are endlessly repeated. Vary the activities to maintain interest and increase success. Also, try interspersing easy tasks (those likely to be done correctly) among more difficult tasks. Studies have shown this procedure to be effective in reducing the likelihood of aggression.[185]
- *Over-plan*. Do not approach a session with only a few ideas or activities to complete. There will be days when the patient finishes everything quickly, and you are left with nothing else to do, or the patient may be having a difficult time (e.g., more confused) and you need some alternate activities more suited to the functioning of the patient that day. Be prepared for anything and confronting a behavior problem will be less likely.
- *Task-analyze*. Try dividing a task into smaller steps. Each step can then be treated as a complete task. Functional skills, such as dressing, hygiene, and grooming, etc., are particularly suited to this approach;[186] however, just about any activity or task can be divided into its component parts. Breaking down a task also increases the opportunity to reinforce the individual for participation and/or completion of the various steps.

BASIC PRINCIPLES

The basic principles of applied behavior analysis are relatively easy to understand. Within a short time, most of the fundamental concepts of behavior analysis, and what is termed operant conditioning, can be grasped. Simply put, behavior analysis focuses on the behavior of people and the environmental influences that precede and follow the behavior, as opposed to their thoughts and feelings. We can refer to these factors as a person's behavioral condition. The components of a person's behavioral condition are the antecedent, the behavior, and the consequence. Behavior analysis attempts to explain the relationship between these components. This relationship is referred to as a contingency. For example, reinforcers are delivered "contingent" upon performance of a certain behavior.

Antecedent

To begin with, all target behaviors (those behaviors to be modified) are preceded by some event in the person's environment. This preceding event is called the antecedent. This event can be a broad-based condition that influences behavior (the setting event) or a more specific stimulus (the stimulus event). In a manner of speaking, the setting event "sets" the stage for the occurrence of the behavior, e.g., fatigue resulting from lack of sleep may be a setting event for behavior problems the next day.[187] Stimulus events are more discrete. For example, a phone ringing means that a behavior (answering the phone) will be reinforced (talking to someone). The antecedent may be an event occurring externally to the person (e.g., lighting, noises, instructions) or internally to the person (e.g., headache, flu, seizure, medication). One word of caution: Even though one has to take into consideration internal antecedents to behavior, the focus of behavior analysis is always on those factors external to the person. Internal antecedents to behavior (e.g., vestibular sensitivity, headache) are best dealt with via medical and therapeutic disciplines within the rehabilitation regimen.

Recently, behavior analysts have increasingly used the term *motivating operations* (MO) to refer to environmental events (antecedents) that establish whether or not a behavior will be affected by a consequence.[188,189] These can include establishing operations that increase effectiveness of consequence and abolishing operations that decrease effectiveness of consequences. For example, if a person is hungry, he or she is more likely to engage in behavior that results in being fed (establishing operation). If the person is not hungry, he or she is less likely to engage in the behavior (abolishing operation).

It is important for staff members to realize that external antecedents are under staff control. Tone of voice, body

language, therapeutic demands, and physical setting are some of the variables that staff can adjust to decrease the likelihood of a behavioral episode.[190–192]

Necessary tasks, however, should not be avoided simply because they can, at times, be antecedents to behavioral episodes. Continued progress toward independence is, often, reliant on the person's participation in such tasks at a very intense level of rehabilitation.[193,194] Avoidance of difficult therapy tasks to reduce "problem" behaviors can be very seductive to staff, but it may simultaneously teach the patient to exhibit more negative behavior as a means of escaping the rigorous demands of therapy.[195] Therapists and behavioral programmers need to survey all environmental antecedents and weigh the advantages and disadvantages of the therapeutic regimen before eliminating or modifying any requirements. Lowering therapeutic expectations because of potential acting out by the person may negatively impact the person's long-term independence. In fact, behavior programs are not a separate treatment; rather they are integrated with the therapeutic plan and run simultaneous to rehabilitative treatment.

Likewise, internal antecedents should be evaluated for other potential treatments that may assist in the person's behavioral improvement. These should not be viewed as reasons to avoid implementation of a behavioral program. Let us say, for example, that a person has a vestibular lesion that causes him to be quite sensitive to motion. One day, after a motor vehicle trip, the person is not feeling well and, during therapy, is quite escalated and trying to avoid participation. He strikes a staff member. Some therapists would be inclined to believe that the individual did not feel well and that the therapist who was struck should not have persisted in treatment. Although this reasoning may seem sound, it is limited by the fact that under no circumstances is it acceptable to strike another person. Thus, the behavioral program would include recognition of the contribution of the vestibular component but would also include a means for de-escalating behavioral agitation and for responding to physical aggression.

BEHAVIOR

An antecedent event is followed by the occurrence of a behavior. If the behavior has been chosen for modification, to either increase or decrease, it is referred to as the target behavior. People with TBI can exhibit a wide variety of behaviors that require intervention. A target behavior must be observable and immediately recordable. The target behavior must also be very clearly defined in terms of observable actions.[196] This is known as an *operational definition*. Two therapists, for instance, can have very different ideas about what constitutes a behavior. For example, take the behavior of physical aggression. Does it include spitting or threatening? What about self-injurious behavior? Should throwing or breaking objects be included? Clear and concise definitions of target behaviors are critical to identifying the behaviors and to implementing programs consistently.

People with TBI can exhibit a number of maladaptive behaviors. Behavior disorders (Table 25.1) can be categorized as those of excess (occurring too often), those of deficit (not occurring often enough), and those of stimulus control (not occurring in the correct context).

Excess behaviors tend to be the most noticeable and, thus, receive the most attention from other persons. Examples of excess behavioral disorders typically seen with the traumatically brain-injured are noncompliance,[197] angry language,[198,199] hoarding,[200] escaping,[201] physical aggression,[202,203] socially inappropriate talk,[204] impulsivity,[205,206] and tardiness.[207] Some other excess behaviors that may be exhibited are sexually aberrant behavior, perseveration, self-abuse, stealing, property destruction, and over-familiarity. These behaviors can be disruptive to other patients, can frighten others, and/or can increase the risk of injury during treatment, thus increasing exposure to legal liability. If severe enough, they can result in a person not receiving proper therapeutic services or, worse yet, being isolated from family, friends, and community in an institutional setting.

Common deficit behaviors of people with TBI are activities of daily living,[208] communication,[209,210] social skills,[211–213] and initiation.[214] Rehabilitation of these skills is of paramount importance in a patient's progress toward more independent living. It is also important that excess behaviors that have been eliminated or reduced through structured behavioral programming be replaced with more appropriate behaviors occurring at a proper rate. Such behaviors will allow the patient access to a wider range of naturally occurring reinforcers, thereby increasing the opportunity for successful generalization and maintenance of skills.

Table 25.1 Behavior categories and examples

Excess	Deficit	Stimulus control
Noncompliance	Compliance	Overfamiliarity
Angry language	Self-control	Public sexual behavior
Socially inappropriate talk	Social skills	Public grooming behavior
Disinhibition	Timeliness	Public discussion of private events
Physical aggression	Initiation	Undressing in public
Escaping	ADLs	
Hoarding		
Tardiness		
Impulsivity		
Sexually aberrant		
Perseveration		
Self-abuse		
Stealing		
Property destruction		
Overfamiliarity		

Stimulus control disorders can occur with any behavior that occurs in the wrong situation (e.g., brushing teeth, hugging another person, etc.). For example, the behavior may occur at the wrong time or place or with the wrong person. The problem of stimulus control as a behavioral disorder has not been fully explored in TBI literature even though there are indications it is a very common problem with this population. Most people with TBI are adults who have already acquired many life skills. Their injury does not necessarily result in loss of the skill but, seemingly, loss of knowledge of the more abstract "situation" in which the behavior should occur. Antecedent or stimulus control behavior programs are tailor-made to positively impact these disorders.

Consequence

Target behaviors are followed by a consequent event that is going to affect the future rate, duration, and/or intensity of the behavior. Consequences are either "reinforcing" or "punishing." Reinforcers will increase and punishers will decrease the future occurrence of the target behavior. Consequences do not inherently possess the quality of being either a reinforcer or a punisher. The effect of the consequent event on the frequency of a target behavior (i.e., whether it increases or decreases the target behavior) defines it as a reinforcer or a punisher. Let us use chocolate as an example. For a person who likes chocolate, its use after the occurrence of a behavior may increase the frequency of that behavior, thereby defining it as a reinforcer. For a person who dislikes chocolate, its use may actually decrease the frequency of a target behavior, thus defining it as a punisher.

There are two types of positive reinforcers: primary and secondary. Primary reinforcers do not require any type of special training to develop their value. Food and water are two examples of primary reinforcers. Secondary reinforcers have gained their value through learning. Examples of secondary reinforcers are praise and money. Secondary reinforcers can be developed by pairing them with a primary reinforcer; for example, if praise is not a reinforcer for a person and food is, food can be paired with praise during behavioral procedures until praise serves as a reinforcer. Food can then be discontinued as a reinforcer.

There are also two types of punishment. One type involves presenting an aversive event following the behavior, and the other removes a positive event following the behavior. For example, getting a ticket for speeding can be an aversive event, and having your driver's license taken away after three tickets is the removal of a positive event.

One of the most misunderstood concepts of behavior analysis is negative reinforcement. It is important that those who work with people with TBI understand this term. Negative reinforcement increases the occurrence of a behavior by eliminating the aversive event after the behavior has occurred.[215] In TBI rehabilitation, being allowed to "escape and avoid" therapeutic tasks is a common example of negative reinforcement.

Another basic principle of behavior analysis is extinction. Extinction does not involve either presenting or taking away consequences to behavior, but, rather, discontinues the reinforcement of a behavior. Not reinforcing the behavior eventually decreases or eliminates the occurrence of the behavior. "Ignoring" is probably the best example of an extinction procedure. Ignoring behaviors that were previously given attention (e.g., complaining, yelling, etc.) can be an effective technique when combined with reinforcement of positive behaviors.

It is recommended that reinforcement programs (or reinforcement combined with extinction) be attempted before implementing a punishment program. Reinforcement programs that teach people "what to do" are generally more effective for long-term maintenance of the desired behavior and do not elicit many of the negative side effects inherent to punishment programs.

Prompting and fading

Teaching behaviors involves prompting to help initiate the behavior. Instructions, gestures, and modeling are all examples of prompting. The self-efficacy theory of Bandura includes as one of its components guided mastery, which can include breaking down tasks into subtasks of easily mastered steps.[216] They are antecedents to the target behavior. The way in which prompting is utilized can have significant impact on how easily a patient learns. A person with language deficits will have difficulty following verbal prompts. In this case, using physical gestures and cues can be more effective. Different types of prompts can be combined to facilitate the desired behavior. Shaping and chaining procedures rely on competent use of various prompting techniques (e.g., backward and forward chaining) to teach new skills.

The goal is for the behavior to occur independently without prompting. The method for accomplishing this is called fading. Fading is the systematic and gradual removal of prompting. If prompting is ended too quickly, the behavior may not continue. A more gradual reduction in prompting is recommended until the behavior is performed independently or with as little prompting as possible. For example, teaching a person with TBI a showering sequence may start with actual physical guidance through many of the steps. Next, some of the physical cues can be reduced to gestures (e.g., pointing) and then to verbal cues. Later, a written checklist can be placed in the shower, listing each step of the showering sequence. The checklist can then be removed, allowing the patient to perform the task independently.

Generalization

Like fading, generalization is an important procedure in developing the independence of a person with TBI or transferring responsibility to primary caregivers and other environments for long-term care, etc.[217] There are two types of generalizations: stimulus generalization and

response generalization. Whereas fading involves decreasing a behavior's dependence on prompts, stimulus generalization reduces a behavior's dependence on the conditions under which it was learned. Most people would agree that rehabilitation takes place in a restricted environment. It is the goal of stimulus generalization that behaviors learned under these conditions be transferred to other settings. For instance, the goal of learning to read in a clinic setting is that it will generalize to reading the newspaper at home or the grocery list at the supermarket. Learning to control physical aggression in the clinic, to give another example, is not as important as the ability to control aggression in the community.

Response generalization involves behaviors rather than the conditions under which they occur. In other words, reinforcing or punishing a specific behavior will also affect similar behaviors. We have seen this occur with patients. A behavior treatment plan that focuses on reducing the most problematic behavior at the same time decreases other less severe behaviors. This experience lends support to the saying, "Worry about the big things and the little things will take care of themselves." Target the most severe behaviors first and the small ones may never require treatment.

BEHAVIORAL DIAGNOSTICS

Prior to writing a behavioral treatment plan, it is essential that a comprehensive assessment of the patient's history, current status, and future goals be performed. The success of a behavior program depends as much on an accurate evaluation of the patient's behavior as on the intervention plan itself.[218,219] The evaluation must analyze all the potential factors contributing to a patient's behavior. The three basic behavioral diagnostic tools are 1) a historical survey, 2) a current status evaluation, and 3) a functional assessment.

Historical survey

Collecting historical information helps the behavior programmer understand how the patient may respond to the rehabilitation process and what he or she expects to gain from treatment.[220] The first half of a historical survey covers a range of demographic data. This includes information on age, sex, marital status, children, parents, friends, religious preference, living conditions prior to the injury, education, work history, and recreational interests. Information we have found to be particularly important is that concerning eating preferences, sleeping patterns, personal likes and dislikes, daily routines, and lifestyle characteristics. Many behavior problems can be averted with an understanding and appreciation of a patient's lifestyle prior to the injury. Requiring the patient to conform to unfamiliar schedules, foods, people, and situations that can be reasonably modified creates a potential setting event.[221,222] As we explained in the previous section, a setting event increases the likelihood of a problem behavior occurring. This can happen when facility staff develop schedules that are easier or less expensive to manage. This inflexibility can contribute to unnecessary behavior problems that are actually more difficult and expensive to manage.

The second half of the historical survey concerns medical and rehabilitation history. It can be helpful for the behavior programmer to know the location and etiology of injury, the elapsed time since injury, and the course of treatment that has been provided. This furnishes the programmer with an idea of the patient's rate of recovery.[223] Additionally, knowledge of a patient's medical history can be beneficial. For example, any diseases, major illnesses, or substance abuse problems that may have occurred before the injury may contribute to the patient's current behavioral status and future prognosis.

Most of the above information can be gathered from medical records, discussions with the previous treating staff, and an interview with the patient and/or significant others, such as family and friends. Contact with prior treatment facilities provides insight into behaviors exhibited by the patient since the injury, under what circumstances the behavior occurred, and staff response. Interviews with the patient and/or significant others help to determine the patient's preinjury behavior pattern, which, in part, determines his or her response to the demands of rehabilitation and life after a TBI.

Current status

TBI usually involves more than just damage to the brain. Many medical and psychological complications can result from TBI. These issues need to be clearly outlined in the behavior plan so that staff can be aware as these complications can also be setting events for behavior problems. For example, if a person is in pain or constantly dizzy, his or her behavioral control will likely be diminished. This is why a comprehensive evaluation of a patient's current status is important.

A current status evaluation reviews a patient's medical and psychological status and therapeutic testing results and examines the relationship of these to behavioral issues. A comprehensive review of the medical status involves looking at the cardiac, vascular, and respiratory systems; orthopedic and muscular capability; the sensory system; bowel and bladder functioning; and other areas of physiological functioning. Of all possible medical problems, medication usually has the most direct relationship to behavior. Medications can profoundly affect behavior; thus, programmers need to be educated and informed on the subject.

A TBI has an impact not only on the patient, but family and friends as well. It is important that programmers understand the dynamics between the patient and significant others. After discharge from rehabilitation, family or friends may be required to carry out behavioral procedures with their loved one or, at the very least, maintain an environment that is conducive to continued learning and development.

One of the most important assessments of current status is a functional skills evaluation. How well is the patient able to perform activities of daily living, such as hygiene, grooming, dressing, and toileting? Is the patient able to cook meals and clean the house? What about community mobility, driving, and shopping? Is the patient able to manage his money? All of these issues are fundamental to levels of independent functioning. They will prescribe the type of living arrangement and level of assistance the patient will require. Also, relearning functional skills can help to replace maladaptive behaviors while reducing the need for aversive procedures.

A review of therapeutic testing results completes the current status evaluation. Standard therapeutic testing includes cognitive, physical, and psychological evaluations as well as a neuropsychological examination. A patient's cognitive level can dictate the type of behavioral procedure that is implemented. Patients with severe cognitive impairment, for instance, will probably not participate in a "contracting" program because it requires more abstract thinking. Physical issues can also directly affect the treatment plan. For example, overcorrection or contingent restraint procedures can be especially ill suited for patients with orthopedic concerns. The neuropsychological examination brings all of the patient's skills and deficits into focus, helping the behavior programmer to design an appropriate treatment plan.

Functional assessment

A functional assessment is central to the design of the treatment plan. Its purpose is to identify the function that each target behavior serves.[224] A functional assessment can be composed of three parts: 1) describing the behavior and its surrounding events, 2) predicting the factors that control the behavior, and 3) testing the predictions by manipulating the identified factors.

A descriptive analysis begins by describing the behavior. This is accomplished by interview and/or direct observation. Direct observations should constitute the primary source of information because anecdotal reports from interviews can be clouded by subjective perceptions. The observations should also occur in a wide range of settings and situations. Nevertheless, in cases in which direct observations are not possible, interviews may be the only method for gathering the information needed to start a treatment plan. Interviews are conducted with those who have direct contact with the patient, such as family members, caregivers, therapists, or paraprofessionals. The interview consists of identifying the target behavior, the conditions under which it normally takes place (antecedent or setting events), what events occur following the behavior (consequence), and what function the behavior serves (e.g., communicating needs). Some behavior problems can be reduced by simply improving the function that the behavior is attempting to perform.[225] If behavior problems are being caused by an inability to effectively communicate one's needs, for example, then improving a patient's communication skills may decrease the problem behaviors. Although indirect assessments, such as interviews, are important to functional assessment, if possible, they should be a secondary source of information.

Functional assessment is usually based on direct observations. The most precise method for collecting observational data is by recording the events surrounding behavioral episodes. An excellent form for organizing this information was designed by O'Neill, Horner, Albin, Storey, and Sprague.[226] Figure 25.1 is a modified version of this form. It includes a place to write in the time of each behavioral event, possible setting events (e.g., difficult task, demands, etc.), the perceived function of the behavior (e.g., attention, avoiding activity, etc.), and the consequence to the behavior. The completed form can then be analyzed for patterns of behavior and the conditions in which they most frequently occur. From this analysis, hypotheses can be formulated regarding conditions maintaining the behavior.

The last step is a functional analysis to test the conclusions drawn from the interviews and direct observations.[227] This involves manipulating specific conditions and observing the level of the behavior occurrences. The idea is that by changing the consequences to a behavior, one may be able to determine the condition maintaining the behavior. Once the conditions have been identified, then a treatment plan can be developed. For example, if physical aggression occurs with a patient 25% of the time while in therapy but only during 5% of the time before starting therapy, one may try allowing the patient "alone time" after completing a specified amount of therapy.

Of course, the time and financial constraints of rehabilitation may make it difficult to always complete this last step of a functional analysis before implementing a treatment plan. However, identifying the conditions that maintain behavior and monitoring the effects of changing these conditions can, at the very least, be utilized during the treatment plan.

BEHAVIOR PLAN FORMAT

A behavior treatment program includes seven major components: 1) short- and long-term goals, 2) precautions, 3) operational definitions of target behaviors, 4) rationale, 5) data collection system and materials needed, 6) staff procedures, and 7) contraindications (Figure 25.2). The behavior programmer must synthesize diagnostic data (historical information, current status, and functional analysis) with goals of the patient, family, treating staff, and payer to create an individualized treatment program. The treatment plan should be written as clearly as possible and in an "easy-to-follow" structure. The programmer has to strike a balance between including all the necessary information and, at the same time, presenting it in a way that is concise and readable. The degree of staff behavioral training will dictate the level of sophistication with which the program can be written and followed with consistency. However, the reality of most rehabilitation environments, whether acute, postacute, or in the home, is that there is a wide range of

Functional assessment	Time					
Behaviors						
Antecedent/setting events						
Demand/request						
Difficult task						
Perceived functions						
Get/obtain						
Attention						
Desired item/activity						
Escape/avoid						
Demand/request						
Activity						
Person						
Consequences						

Figure 25.1 Functional assessment form.

behavioral competence. The Behavior Analyst Certification Board (BACB)* was created to develop, promote, and implement a voluntary national certification program for behavior analyst practitioners. It also serves as a resource for identifying certified practitioners and training courses for staff. The Professional Crisis Management Association (PCMA)† has also been providing crisis management and behavior analysis training, certification, consulting, and technology-based solutions for individuals and organizations. However, even after extensive training, there are significant differences in the degree of "natural" ability among staff to carry out effective behavioral treatment. Differences in natural ability can be due to difficulty in controlling one's own behavior, lower sensitivity to nonverbal signs exhibited by a patient, and personal attitudes about the patient and/or behavior program. This being the case, a step-by-step procedural outline, combined with close monitoring of staff performance, is the most practical format with which to run behavior treatment plans.

Goals

Behavior treatment goals are separated into short- and long-term goals. Short-term goals are objectives that define

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† Professional Crisis Management Association (PCMA), Copyright 2015.

Behavior treatment plan

Client name: C. G.
Program start date: 11-30-03
Implemented by: Clinical therapists and staff aides

Goals:

Short-term goal: To decrease physical aggression by 5% of total intervals from last month.

Long-term goal: To increase independent living scale (ILS) score to more than 80/100 pts. (min-mod. supervision).

Evaluation of goals: Weekly summary of interval data.

Target behaviors:

Primary:

Physical aggression (PA): Attempting to and/or striking out with an object or body part; may include hitting, kicking, pinching, grabbing without permission, scratching, throwing items at someone, etc.; includes attempted or actual contact; does not include verbal threats or invasion of personal space.

Property destruction (PD): Ramming, throwing, tearing, striking, or breaking property (even if accidental; or attempts to do so), property does not have to be damaged.

No cooperation (none): Did not participate in therapy at all and exhibited at least one target behavior. May be in therapy area, yet did not attempt any activities.

Secondary:

Angry language (AL): Cursing, yelling, threats, hostile language, demands delivered with increased volume (above conversational level) lasting more than two seconds.

Refusal to work (R): Active or passive statements or actions meant to evade, start, interrupt, or stop therapy tasks or directives; must be more than one minute; does not include slow processing time or lack of ability.

Escaping (E): Attempted to and/or left place of required activity.

Partial cooperation (part): Attempted and/or completed some therapy tasks as directed. Displayed one or more target behavior(s), but was able to be redirected to task or attempted the task prior to any behavior episode.

Full cooperation (full): Attempted and/or completed all therapy tasks as directed. No target behaviors displayed.

Figure 25.2 Example of behavior treatment plan. (*Continued*)

the desired measurable change in the target behavior. A specific time frame for accomplishing the objective should be clearly stated. For example, "Physical aggression (the target behavior) will be reduced to 5% of the total recorded intervals within 30 days." Short-term goals help the patient and staff focus on tangible achievements while continuing to strive toward long-term goals.

Long-term goals, on the other hand, describe the projected functional outcome of the treatment plan. For example, "The patient will increase independent living to a minimal supervision level (group home) or will be able to work in a part-time volunteer employment position." Long-term goals are to be defined by the patient, family, caretakers, funding source, and other responsible parties.

All goals and objectives should include three parts: 1) how they will be assessed, 2) how often they will be reviewed, and 3) what type of report will be generated. Many accrediting or regulating agencies, such as the Commission on the Accreditation of Rehabilitation Facilities (CARF)*, require these guidelines for accreditation. The assessment of goals can be accomplished by many public or in-house rating systems. For example, long-term goals of disability level can be gauged by the Disability Rating Scale.[228] Short-term goals can be evaluated by a standard data collection system (e.g., frequency count, time-sampling, etc.). Short- and long-term goals should include a statement concerning the frequency of review (e.g., weekly, biweekly, monthly) and what type of report will be produced.

Target behavior

Target behaviors are the focus of the treatment plan. They are the behaviors that are interrupting therapy, impeding

* CARF International, Copyright 2015.

Materials and data collection:

1. 15-minute interval data sheet.
2. Two-minute therapy chart.
3. Two-minute board with countdown timer.

Treatment procedures:

Outline: This program will consist of several key components including: 1) a two-minute fixed interval DRO, 2) primary target behaviors of PA and PD, 3) a reward contingent upon completion of the five, two minute blocks of therapy with no occurrence of the target behaviors, 4) a graduated guidance program contingent on the occurrence of non-compliance, and 5) relaxation practice each hour.

Relaxation: Begin each hour with two minutes of timed relaxation practice. Tell C. G. to "take a couple of minutes to relax." Ask him to close his eyes, take a deep breath, and let his mind and muscles relax. Make every effort to keep the surrounding therapy area quiet during his relaxation time.

DRO: Following the relaxation period, post the two-minute board on a straight back chair near the task area where C. G. can see it clearly. Inform him that when each of the boxes has an "X" in it, he can go outside. Set the timer for two minutes and begin therapy. Each time the timer sounds and C. G. has not exhibited a primary target behavior, "X" out a box on the board, quickly reset the timer, and continue therapy. Try and keep therapy tasks flowing comfortably while maintaining awareness of the timer. Immediately after the final (fifth) box has been "X'd", state to C. G. "Great, you stayed calm; we can go now" and take him for a short walk outside. Have C. G. walk himself during the walk unless he asks for assistance. Reflect to him that this is his time and he has earned it. After about 3–5 minutes, redirect C. G. back to therapy. Do not allow him to manipulate or slow his return to therapy. Assist as needed. Immediately reset the timer and repeat the above sequence.

Graduated guidance: If C. G. displays non-compliance (i.e., refusing to start a task), **immediately** provide hand-over-hand guidance. Have tasks available that C. G. can be physically guided through. For example, tasks requiring pointing, reaching, touching, etc. As soon as non-compliance begins, start prompting the current task or immediately switch to an activity requiring motor involvement. Provide guidance until C. G. begins complying, then fade physical prompting. Once guidance has been discontinued, return to the task and/or approach used before the behavior occurred.

Figure 25.2 (Continued) Example of behavior treatment plan.

progress, endangering others, disrupting activities, or otherwise interfering with a person's ability to live independently in the community. They can be behaviors of excess (e.g., physical aggression), deficit (e.g., hygiene and grooming), or stimulus control (e.g., public sexual behavior).

Each target behavior must be operationally defined. The operational definition describes what the behavior "looks like" in objective, observable terms. For example, labeling a target behavior "physical aggression" without an operational definition leaves it wide open to interpretation. The more interpretation is allowed in a behavior program, the less consistent it will be. Not only does an operational definition describe what a behavior "is," it also describes what it "is not." For example, physical aggression could be defined as any attempted or actual hit, strike, kick, pinch, or grab by the patient, not including spitting.

Operational definitions sometimes require that the context in which the target behavior will occur be identified. For example, "hand waving" is only a problem when it interferes with writing activities. The definition may also need to include the duration or rate at which the behavior must occur before it is considered a target behavior. For example, refusing to participate in therapy for more than 30 seconds may be the minimum criteria for "noncompliance."

Rationale

This section briefly outlines the reasons why an individual may require a behavior treatment program. Information such as a review of assessment and/or baseline data results, direct observations, and interviews with relevant caregivers and family can be discussed. It may be important to describe the behaviors of concern and the impact these behaviors may have on the individual's future access to social reintegration. A summary statement regarding why the program has been developed will help those implementing the program better understand what led to the plan.

Materials and data collection

The third section of a behavior treatment plan outlines all the materials required to carry out the prescribed procedures and the data collection system for tracking the rate and/or duration of the target behavior. Many behavior treatment plans require specific materials for implementing procedures. For example, a stopwatch may be needed for a "differential reinforcement of other behavior" program that calls for reinforcing the patient after a specified period of time in which the target behavior does not occur. Any supplies or items that are used to implement the treatment plan

(e.g., timer, tokens, tape recorder, etc.) need to be described in this section.

The second half of this section describes the data collection system. All behavior programs should have a procedure for gathering information that will be used to determine the effect of the treatment plan. The data collection and graphing section of this chapter details methods for systematically recording and analyzing behavioral data. Without consistent data collection, it is difficult to ascertain whether or not the program is working. Anecdotal reports (i.e., verbal feedback from staff) are usually not reliable enough, due to their subjectivity, to make important decisions concerning the effectiveness of behavior programming. Frequency, interval, duration, or time-sampled data of operationally defined target behaviors gives the behavior programmer ample information which, together with staff feedback, will allow for better treatment decisions.

Treatment procedures

The procedures section of the treatment plan describes the steps of the behavior program. It outlines the staff's response to the target behavior (consequence) and arranging of environmental conditions prior to the behavior (antecedent). The section on behavior plan procedures details a variety of behavior treatment plans.

The treatment plan describes each step a staff member is to take before and after the occurrence of the target behavior. Every step needs to be described in clear, concrete terms that can be understood by a wide range of people, including the patient, staff, and family. More often than not, the success of a program rests on the ease with which the procedures can be followed. Figure 25.2 is an example of a completed treatment plan.

Contraindications

Behavior programs are not without "side effects." As programs are implemented, individuals may react in a number of ways. This section is the programmer's opportunity to consider what reactions may be anticipated and how staff can best respond. Frustration, reactive aggression, elopement, and verbal agitation may occur during implementation of the program. It is important to consider how the individual may behave so those providing the treatment are less surprised and can anticipate how to respond so as to maintain program integrity.

BEHAVIOR PLAN PROCEDURES

The staff member responsible for writing behavior programs has many designs from which to choose (Table 25.2). The types of behaviors exhibited by the patient, the setting for implementing the program, and the level of staff skills and experience are all factors to be considered in choosing the most suitable behavior program. Once these factors have been identified and weighed, one can then choose a treatment procedure that is *accelerative* (designed to increase the frequency or duration of a target behavior), *decelerative* (designed to decrease the frequency or duration of a target behavior), or *complex* (having characteristics of both accelerative and decelerative programs). Combinations of these procedures, in a multicomponent approach, can also be used simultaneously to increase the speed of and maintain behavioral change.[229]

We will outline procedures for the most common behavior programs and provide illustrations (for most procedures) of actual cases encountered in behavioral treatment. Some of the techniques we will not be covering in this chapter are group-based programs, peer-administered contingencies, biofeedback, and cognitively based treatment (e.g., stress reduction, problem-solving skills, self-statements, etc.). These methods are either not often used, not practical for people with TBI (e.g., group-based programs, peer-administered contingencies), or fall more into the realm of counseling (e.g., cognitively based treatment).

Accelerative programs

POSITIVE PROGRAMMING

Positive programming is nothing more than teaching individuals new skills through the use of reinforcing consequences.[230] Activities of daily living, functional communication, and social skills training are all examples of positive programming. This technique is familiar to most of us since we have been exposed to learning new skills (e.g., reading) and being rewarded for our performance (e.g., grade).

An advantage of positive programming is that it is constructive in nature. It teaches people "how to do something." Positive programming helps to reduce undesirable

Table 25.2 Behavior program treatment procedure designs

Accelerative	Decelerative	Complex	Other
Positive programming	DRI	Contracting	NCR
Shaping and chaining	DRO	Stimulus control	
	DRL	Token economy	
	Overcorrection		
	Stimulus change		
	Stimulus satiation		
	Time out		

behaviors that are incompatible with the new skill (e.g., the social skill of shaking hands is incongruous with hitting).[231] Generalization and maintenance of skills taught through positive programming are also, often, supported by naturally occurring contingencies (e.g., learning to verbalize allows one to express and receive one's needs).

A disadvantage of positive programming can be its lack of quick results; positive programming takes time. Because of the tremendous costs involved in the rehabilitation of people with TBI, pressures are exerted on rehabilitation programs to bring about behavioral change as quickly as possible. This does not infer that positive programming should be excluded—rather that efficient programming must be developed to meet the needs of payers. To help accomplish this, positive programming can be integrated with other behavior programs that focus on decreasing undesirable behaviors. The result should be increased efficiency and rate of behavioral change.

Case Illustration

H. H. was a 32-year-old male injured in a motor vehicle accident. H. H.'s physical and cognitive skills were severely impaired. Expressive language, in particular, was extremely difficult. Most of his severe behavior, which included physical aggression and self-injurious behavior, occurred when his wife would leave for home at the end of his day at the clinic. When she would inform him she was leaving, he would start yelling, attempt to attack her or anyone intervening, and throw himself out of his chair. On one occasion, he stabbed himself with a pencil that was lying nearby.

The program for reducing his aggressive behavior was to replace it with more appropriate social and communication skills. H. H. was taught to wave goodbye to his wife before she departed for the evening. This was accomplished by having the patient, during counseling sessions, practice saying goodbye to a videotaped presentation of his wife. If he completed the sequence correctly and without any negative behavior, he was allowed to color in one section of a black-and-white drawing of his house. The drawing was divided into seven sections. When he completed coloring in the seven sections, he earned a supervised weekend home visit. Once he succeeded at the videotape presentation and earned a visit home, the patient practiced saying goodnight to his wife in person. The same reinforcement procedure was used again. Seven successful trial sessions resulted in a weekend home. H. H. successfully completed both training procedures within approximately 30 days and never presented the problem again during the rest of his stay in rehabilitation. The more appropriate social skills of saying goodnight and waving goodbye had replaced the maladaptive behaviors of physical aggression and self-injurious behavior.

SHAPING

Shaping refers to the reinforcement of gradual approximations to a target behavior and is, generally, used with behaviors that do not require urgent change. For example, if a therapist wants a patient to remain seated during the therapy session, she may start by reinforcing the patient for remaining seated for five continuous minutes at a time. Once the patient is able to accomplish this consistently, the time can be increased to 10 minutes, and so on, until the patient remains seated the entire session. Although shaping is used primarily for skill building (e.g., learning a single step of a dressing procedure, such as pulling one's shirt all the way down), it can also be used to modify maladaptive behaviors. For example, if a patient is constantly late for therapy, he or she could be reinforced for approximating closer correct arrival times to therapy.

CHAINING

Chaining, often confused with shaping, involves teaching a sequence of steps to a task.[232] The basic sequences in which such a task may be taught are termed forward chaining, backward chaining, and whole task method.[233] For example, putting on a pullover shirt would involve teaching a person the steps of 1) putting his arms through the sleeves, 2) pulling the shirt over his head, and 3) pulling the shirt down over his body. In forward chaining, one would begin teaching with the first step (putting arms through the sleeves), then, combine steps one and two, and finally connect the sequence of steps one through three. In backward chaining, one actually begins teaching the last step first (e.g., pulling shirt down), then, combines steps three and two, and finally steps three through one. In the whole task method, the most common teaching technique, the entire sequence (step one to step three) is taught each time. Evidence is not clear as to which of these methods is most effective; however, backward and forward chaining is usually used if one is trying to reduce the number of errors produced by the patient during learning.

Case Illustration

K. T. was a 38-year-old female who was injured in a motor vehicle accident. The injury left K. T. with severe cognitive and behavioral problems. Her most difficult behavior was an intense motor restlessness and inability to sustain attention. She was constantly moving her legs and arms and would exit from therapy every few minutes. A shaping program was introduced to try to increase her ability to sit in a chair and participate in therapy. The procedure started with having K. T. sit on the floor for 30 seconds. If she completed this successfully, she was allowed up, and a poker chip token was placed in a circle on a board with 10 total circles. When all 10 circles were filled with a token, K. T. was taken for a walk around the clinic or outside. After she mastered floor sitting for 30 seconds with minimal failures, she

was instructed to sit in a chair for 30 seconds. The same procedure was repeated. The 30-second time period was systematically increased over several weeks with the structured introduction of "tabletop" activities, until she could sit at a therapy table for 45 minutes and work on therapeutic tasks without exiting. K. T.'s ability to sit quietly and work on cognitive activities had been shaped to a length commensurate with most patients participating in rehabilitation. The same program was used with K. T. in her living environment to help her sit at the dining table and finish eating a meal.

Decelerative programs

DIFFERENTIAL REINFORCEMENT OF INCOMPATIBLE BEHAVIORS (DRI)

DRI involves reinforcing behaviors that are topographically different from or incompatible with the target behavior.[234,235] For example, the behavior of keeping one's hands in the lap or to the side is topographically different from hitting oneself. The production of the topographically different behavior actually competes with or disallows the production of the target behavior. Thus, reinforcing the patient for keeping his hands in his lap or to his side is said to differentially reinforce an incompatible behavior.

Careful monitoring of behaviors during a DRI program is required to make certain that the target behavior is actually decreasing and not only that incompatible behaviors are increasing. Using the above example, one could imagine that the patient's time with hands in his lap or to his side (incompatible behaviors) could increase, and self-hitting (target behavior) could remain unchanged. If this occurs, use of a differential reinforcement of other behaviors (DRO) program may be more effective.

Case Illustration

E. N. was a 43-year-old male who was injured in a motor vehicle accident. E. N. exhibited a variety of tic-like behaviors. He would touch or pick at his nose and face and grab his crotch area constantly throughout the day. As you can probably guess, social interaction with others was severely limited by these behaviors. A DRI was implemented to help reduce these socially unacceptable behaviors. During therapy sessions, E. N. was reinforced with tokens for keeping his hands either on the table or engaged in hand-involved therapeutic tasks. The tokens were exchangeable for certain privileges in his living environment. Over a period of several months, E. N.'s tic-like behaviors decreased to a socially acceptable level. His inappropriate behavior (i.e., touching nose, face, or groin) had been replaced by incompatible behaviors (i.e., hands on table or engaged in a task). It was not possible for E. N. to exhibit both behaviors at the same time.

DIFFERENTIAL REINFORCEMENT OF OTHER BEHAVIORS (DRO)

DRO is defined as reinforcing any behavior other than the target behavior for a specific interval of time.[236,237] For example, if the target behavior is physical aggression, the therapist would reinforce the patient at the end of every designated time interval in which the physical aggression was not exhibited. One can keep the time intervals absolute (e.g., every 15 minutes) or relative (e.g., resetting the clock after every occurrence of the target behavior). If the patient exhibits physical aggression, the clock is reset for another 15 minutes. Once there is an increase in the number of intervals in which aggression does not occur or when it is occurring at a predetermined lower rate, the interval size can be systematically lengthened and eventually eliminated.

There are, however, a few precautions to take when implementing a DRO program. DRO programs are not designed to reduce high-rate behaviors. High-rate behaviors do not allow enough time to reinforce the patient between episodes of the targeted inappropriate behavior. Also, by their nature, DRO programs reinforce any other occurring behaviors. Therapists need to be aware that they may inadvertently reinforce another undesirable behavior.[238] As with many decelerative programs, DRO procedures do not teach people new skills and, thus, are more effective if implemented in concert with positive programming.

Case Illustration

C. I. was a 27-year-old male who was injured in an industrial explosion. As a result of the accident, C. I. had severe cognitive deficits and could not ambulate independently. He also had severe aggressive behavior problems that were significantly interfering with all rehabilitative therapy. C. I. exhibited hitting, kicking, biting, yelling, exiting, and noncompliance in therapy. A DRO program was started to reduce the abovementioned behaviors. C. I. was required to participate in the therapy task for a total of 2 minutes without any of the target behaviors. If he was successful, an "X" was marked over one of five squares on an erasable dry ink board. A picture of an outdoor scene was attached to the board at the end of the five-square sequence. Any time C. I. displayed one of the target behaviors, the clock was reset to zero, and a new 2-minute interval would begin. As soon as five squares were marked, C. I. was taken for a walk outside of the clinic (the identified reinforcer). When he was able to complete 2-minute intervals approximately 80% of the time without resetting, the time was increased to 5 minutes, and then to 10 minutes. Eventually, C. I. was able to participate in therapy for a full 45 minutes before taking a break. He was being reinforced for any behaviors "other" than the target behaviors.

DIFFERENTIAL REINFORCEMENT OF LOW RATES OF BEHAVIOR (DRL)

DRL programs provide reinforcement if a specified interval of time has elapsed since a target behavior last occurred or if a specified number of occurrences of the target behavior have occurred during the interval.[239,240] For example, if the target behavior is yelling, a DRL program may state that a patient is to be reinforced for each 15-minute interval of time that passes since yelling last occurred or for each time interval in which the target behavior occurs below a certain rate (e.g., five occurrences or less of yelling every 15 minutes). The time intervals can then be lengthened (e.g., from 15 minutes to 30 minutes) or the number of occurrences allowed can be decreased (e.g., five occurrences to two occurrences every 15 minutes) until the target behavior is eliminated or reduced to an acceptable level. Baseline data must be collected to determine either the initial time interval length or the initial number of occurrences to be allowed for the patient to receive a reinforcer. For example, if a behavior is occurring four times per hour, an appropriate interval length may be 15 minutes or reinforcement for every 15 minutes that the behavior occurs only once. This interval length will ensure initial success by the patient and help develop reinforcer strength.

Some of the advantages of DRL programs are that interval times can be adapted to fit therapy sessions (e.g., 45-minute sessions can be divided into 15-minute intervals), and high-rate behaviors, for which DRO programs are not designed, can be systematically reduced. Like DRO programs, however, DRL programs do not teach new skills. Instead, the focus is on reduction of maladaptive behaviors. DRL programs, therefore, should be supplemented with positive programming of some type.

Case Illustration

K. C. was a 36-year-old male who was injured when the bicycle he was riding was hit by a car. K. C. presented several behavior problems, including verbal and physical aggression. If he displayed any target behavior, the DRL program stated he must go to his kitchen and remove one of four keys hanging on a corkboard. If, at the end of 3 days, he still had one key remaining, he could unlock a box and choose one of several available reinforcers (e.g., $10). When K. C. was able to earn his 3-day reinforcer three consecutive times, the reinforcer period was increased to 4 days and so on until it reached a 1-week reinforcer time period. The number of keys was then reduced until only two keys were available. This meant he could only exhibit one target behavior per week and still earn a reinforcer. K. C.'s target behaviors had been systematically reduced to lower rates.

OVERCORRECTION

There are two types of overcorrection procedures: restitutional and positive-practice overcorrection.[241,242] Restitutional overcorrection requires that a person returns the environment (e.g., therapy room) to a state better than before the behavioral episode. For example, if an agitated patient knocks over a chair, he or she is required to pick up not only that chair, but to straighten all other chairs in the room as well.

Positive-practice overcorrection requires repeated practice of an appropriate behavior. For example, if a patient walks with poor posture, he or she may be asked to practice walking with upright posture for specified periods of time.

Overcorrection can be an alternative to other, more punitive punishment procedures. The disadvantages are that overcorrection can be time-consuming and can elicit aggression in circumstances in which overcorrection requires physical guidance to obtain compliance.

Case Illustration

O. H. was a 42-year-old female who was injured in a motor vehicle accident. She had spent approximately 1 year in a locked psychiatric institute on multiple psychoactive medications prior to admission for rehabilitation. She exhibited behaviors of yelling, hitting, stripping, exiting, and noncompliance with therapy. Although continent of bowel and bladder, O. H. would periodically urinate small amounts on furniture during therapy. A restitutional overcorrection program was implemented to reduce this behavior. If O. H. urinated on a chair, she was required to change her clothing, put the dirty clothes in the wash, clean the chair that was soiled, and wipe off all other chairs in the room. O. H.'s inappropriate urination ended within a few weeks.

Case Illustration

S. D. was a 29-year-old female who fell into a diabetic coma and suffered anoxia. S. D. displayed yelling and noncompliance to therapy and was also incontinent of bladder. A positive-practice overcorrection program was started to reduce her incontinence. If S. D. was incontinent between her scheduled bathroom visits, she was required to go to the bathroom and practice a series of five correct "toileting" sequences (i.e., adjust clothing, sit on toilet, clean self, get up, adjust clothing, wash hands). After several months, S. D. was continent of bladder and able to live in a supervised group home.

STIMULUS CHANGE

Stimulus change is the sudden introduction of an unrelated (nonfunctional) stimulus or change in stimulus conditions that results in a temporary reduction of the target behavior.[243] For example, clapping loudly once while a patient is engaged in yelling or suddenly shouting the patient's name

if he is engaged in aggressive behavior may cause a lapse in the behavior.

An advantage of stimulus change programs is that their effectiveness can be determined very quickly. There is no need for any long-term assessment of the program. The disadvantage of a stimulus change program is that its effect may be temporary (startle effect), and/or the patient may quickly adapt to the stimulus event and return to the maladaptive behavior. Stimulus change programs are almost exclusively used as "emergency" programs to quickly stop destructive behavior.

STIMULUS SATIATION

Stimulus satiation programming allows unrestricted access to the reinforcer of an undesirable behavior.[244] The unconditional availability of the reinforcer will eventually weaken its relationship to the target behavior. Stimulus satiation weakens the reinforcer through the process of satiation (complete satisfaction) and deprivation of other reinforcers.[245]

Case Illustration

C. F. was a 32-year-old male who, while working on a rooftop, was electrocuted and fell. C. F. exhibited a number of severe behavior problems; however, one unusual behavior was his obsession with staying on the toilet. When cued to leave the bathroom, C. F. would become extremely agitated and start yelling. If anyone tried to help him out, he would become physically aggressive. His time in the bathroom was becoming increasingly longer and his behavior more severe. A stimulus satiation program was implemented to reduce his time in the bathroom. The program allowed the patient to stay in the bathroom and on the toilet for as long as he desired. Over a period of 2 weeks, C. F.'s time on the toilet increased to over 19 consecutive hours in 1 day. The following 2 weeks saw his time in the bathroom decrease gradually to what would be considered "normal" lengths of time. Unlimited access to "toilet time" eventually weakened its reinforcement quality (i.e., satiation).

TIME OUT

Time-out procedures[246] (also known as contingent withdrawal) can be either nonseclusionary or exclusionary. Nonseclusionary time out involves withdrawing attention from a person while remaining in his or her presence. Exclusionary time out consists of removing the person from a reinforcing environment following the occurrence of a target behavior. For example, when a patient exhibits verbal threats, one can either ignore the statements (nonseclusionary) or remove the patient from the area (exclusionary). Time-out procedures are more effective if the reinforcer sustaining the behavior is attention from others. A third type of time-out procedure, seclusionary, involves the use of a time-out room when the patient exhibits a specific target behavior. Strict guidelines need to be followed to safely operate seclusionary time-out procedures.[247]

- The duration of seclusionary time out should be as brief as possible (e.g., 1 to 5 minutes).
- The room should be well lit, ventilated, and free of dangerous objects (e.g., light fixtures).
- The room should have provisions for visually monitoring the person.
- The room should not be locked, only latched.
- Records should be kept for each use of the time–out room. At a minimum, records should include the patient's name, description of the behavioral episode, and start and end time of the procedure.

An advantage of time-out procedures is that they are easy for staff to understand. The disadvantage is that, in reality, time-out procedures can be very difficult for staff to implement. It is extremely difficult for staff to completely ignore a patient's target behavior (e.g., threats, cursing) 100% of the time. If the target behavior is not ignored, it can be inadvertently intermittently reinforced. Intermittently reinforced behavior is actually strengthened. Also, a patient should not be removed from the therapy area as part of an exclusionary time-out procedure if the behavior is to escape and avoid therapy. Time-out procedures should always be combined with positive, skill-building procedures (e.g., positive programming, shaping) to develop functional skills to replace the behavior being extinguished.

Case Illustration

L. I. was a 24-year-old male who was injured in a motor vehicle accident. L. I. exhibited behaviors of verbal aggression, threatening behavior, and noncompliance. He had sustained a MTBI. If L. I. did not want to participate in a therapeutic activity, he began by arguing and, then, escalated to yelling and threatening physical aggression. A nonseclusionary time-out procedure was started to reduce his aggressive behavior and increase his compliance with therapy. Attention from staff was the identified reinforcer. Any time that L. I. began arguing and refusing to follow instructions, therapists were instructed to inform L. I. that they were going to their office and would return when he was ready to stop yelling and cooperate. Other staff members were also instructed to ignore L. I. if he was not with his therapist during therapy time. Cooperation increased to an acceptable level over a 2-week period.

Complex programs

CONTRACTING

Contracting is a technique that involves a written agreement between the patient and another person.[248,249] A key

to behavioral contracting is that the elements of the contract are agreeable and understandable to both parties. Contracting can shift the focus of therapy away from the demands of a therapist to one of cooperative problem solving. Patients may be more likely to follow therapeutic guidelines when they feel part of the decision-making process and can see behavioral steps and reinforcers outlined in a written format. Contracting should include a definition of the target behavior or goal, how the behavior or goal will be measured or monitored, rewards for following the contract, and the signatures of both parties. Contracting can work well for behaviors such as tardiness, cooperation, and quality of performance, which are typically thought of as involving "higher" levels of self-control.

Case Illustration

T. K. was a 36-year-old female who, while working as a junior high teacher, was injured when hit in the head by a student. T. K. was diagnosed as having "mild" head injury. Most of her symptoms were related to psychological functioning and high-level abstract thinking. One specific symptom that caused her difficulty was a sensitivity to light. Following the injury, she could not tolerate bright light, including indoor fluorescent lighting. She developed a habit of wearing dark glasses, both outdoors and indoors. As therapy progressed, she still felt the need to wear dark glasses indoors. T. K. stated that she wanted to stop wearing dark glasses inside; however, she could never fully cooperate. Various procedures were attempted to reduce her dependence on dark glasses, but none worked. Contracting was finally adopted. T. K. signed a contract stating she would cooperate with systematically reducing her time wearing glasses based on gradually increasing periods without "dark glasses on." Once the goals were outlined and the contract signed, full cooperation from T. K. was achieved. She completed her rehabilitation and was discharged without the need to wear dark glasses indoors.

STIMULUS CONTROL

Stimulus control programming involves bringing the target behavior under the control of a specific stimulus or set of conditions.[250] Many behaviors are deemed acceptable or unacceptable based on the circumstances under which they occur. Sexual intimacy, for example, is considered an acceptable behavior if it occurs between consenting adults in the privacy of their home. If it occurs at the supermarket or on a public bus, however, it would not be considered acceptable. The goal of stimulus control programs, then, is to bring behaviors that may be occurring at the wrong time, place, or frequency into more appropriate or more easily controlled stimulus conditions.[251] Behaviors are brought under stimulus control by reinforcing the target behavior at the time and/or location at which the behavior should naturally or acceptably occur (e.g., masturbating in the bedroom rather than in public). Behaviors can also be brought under a specific stimulus control that is then progressively reduced, decreasing the frequency of the behavior as access to the stimulus decreases. Stimulus control programs are considered positive in nature because the behavior is being reinforced, in most cases, for occurring in a more appropriate environment or time.

It is not recommended that stimulus control programs be used with more violent or destructive behaviors (e.g., physical aggression, self-injurious behavior). Severe behaviors are potentially dangerous to the patient and others and, thus, are not acceptable even at low rates of occurrence or in selected settings.

Case Illustration

D. K. was a 37-year-old male who was injured in a motor vehicle accident. As a result of severe brain injury, D. K. displayed physical and verbal aggression, exiting, and noncompliance with therapy. His verbal behavior (i.e., threats, cursing, and yelling) was his predominant problem. A stimulus control program was implemented to reduce verbal agitation. A therapy room was set aside as the stimulus control environment. A lamp with a blue incandescent light bulb was placed on the table to increase the uniqueness of the room. To begin with, all therapy sessions were done in this room. If D. K. exhibited any verbal target behaviors, he was reinforced with a variety of edibles and verbal praise. To ensure a high reinforcer rate, if D. K. did not exhibit a target behavior within 60 seconds, he was prompted by the staff to "please yell." In contrast, when D. K. was outside of the room (for walks, bathroom breaks, etc.), all target behaviors were ignored. After 3 weeks of using the stimulus control room exclusively for therapy, D. K. was systematically moved to conventional rooms at a rate of one per week. Again, he was reinforced for exhibiting target behaviors only in the stimulus control room whereas target behaviors were ignored in all other conditions.

TOKEN ECONOMIES

Token economies require the use of secondary reinforcers (tokens) that a person has earned and that can be traded later for something of value to the person.[252] For example, plastic poker chips are commonly used as tokens that are earned for positive behaviors, such as compliance with therapy. Patients can then trade in the chips daily, weekly, etc. (depending on the reinforcement interval length required) for any activity, privilege, or item identified as a reinforcer (e.g., dining out, movies, money). One can also include a *response–cost* aspect to a token program. This involves losing tokens for exhibition of specific behaviors. For example, a patient may earn tokens for compliance with therapy and lose tokens for exhibiting any physical aggression.

The most difficult aspect of a token program is deciding the value of each token and how often the patient can earn it. Baseline data on the frequency of the target behavior is necessary to determine the potential earning power of the patient. Token programs should be neither too easy nor too difficult for a patient. An earning rate of about 70% to 80% is probably a good rule of thumb. Advantages of token programs are that they provide for structure, concrete feedback, delay of gratification, and ease of use across many settings (e.g., therapy room, community, home).

Case Illustration

S. X. was a 28-year-old male who was hit by a motorist while working as a motorcycle highway patrolman. S. X. suffered a severe brain injury that left him with significant cognitive and physical deficits. With the exception of physical therapy, S. X. was limited to using a wheelchair for mobility. While sitting, S. X. would let his head fall forward and begin drooling. He would also let his left hand pull up to his chest instead of keeping it in a more neutral position on his lap. A token program was started to decrease the abovementioned behaviors. He could also earn bonus tokens for each 15-minute interval in which he added inflection to his "monotone" voice. A response–cost element was added to decrease his habit of transferring out of the wheelchair without supervision. He was given a "transfer ticket," which cost him tokens if anyone witnessed him transferring without another person present. Tokens were earned on a 15-minute-interval basis (determined by baseline data on the rate of target behaviors) and could be cashed in for food outings and extra walking time. By time of discharge, S. X.'s drooling and hand position had been resolved, and he was placed in a semi-independent living environment and a part-time position with the police force as an office clerk.

Other programs

NONCONTINGENT REINFORCEMENT (NCR)

NCR procedures involve the delivery of reinforcers on a time schedule that is not contingent upon the subject's behavior.[253,254] This is different from a traditional, contingency-based model of reinforcement. For instance, if "attention from others" is the identified reinforcer, attention will be delivered to the patient on a fixed schedule (e.g., every 15 minutes), independent of the patient's behavior. Whether the patient acts inappropriately or appropriately, the reinforcer "attention" will be given to the patient every 15 minutes.

NCR has some advantages over other reinforcement programs. It requires little in the way of monitoring whereas other programs require constant observation of the patient's behavior. This can be an important factor in situations in which staffing levels are less intensive, such as long-term care environments or programs that don't offer one-to-one therapy-to-patient treatment ratios.

Case Illustration

C. I. was a 40-year-old male with TBI participating in a long-term care program. C. I. suffered a brain injury as a result of a motor vehicle accident 13 years prior to his admission. Although suffering from severe cognitive deficits, C. I.'s aggressive behavior toward others and himself was of primary concern. C. I. participated in structured individual- and group-oriented activities during the day and in a residential setting during the evenings and weekends, relearning activities of daily living.

Physical aggression and self-injurious behavior were identified as the target behaviors and "attention" as the maintaining reinforcer. Attendants delivered attention every 30 minutes, independent of behavior, for the patient's waking hours. The attention sequence consisted of spending 3 minutes in social conversation with C. I., after which he was redirected to an activity. Implementation of the NCR program resulted in physical aggression occurring four times less often and self-injurious behavior two and a half times less often than prior to the program.

Summary

The design of an effective behavioral program may require combining a number of the procedures just described. No single design can be used universally. Consequently, it is often necessary to begin with one procedure and switch to another when the first plan fails or loses its effectiveness.

Recent studies have also stressed the importance of contextual control in choosing treatment plans.[255,256] Contextual control recognizes the role that context (stimulus setting) plays in altering the effect of behavior programs. A treatment plan designed to modify behavior in one environment may not be effective in another.[257]

DATA COLLECTION AND GRAPHING

Behavior programming requires a procedure for systematically recording and graphing behavior data. Decisions regarding the effectiveness of treatment plans should be data based and this demands comprehensive data collection. When possible, collect data throughout the entire day and evening—not just in structured settings. Behavior data from the home and community are just as important as those from a school or rehabilitation facility. Long-term maintenance is questionable if behavior changes do not

generalize to other, more natural environments. This section covers methods of data collection, graphing, analysis of data, and the use of computer technology to assist in data management. Although comprehensive data collection and graphing can be time-consuming and somewhat rigorous to implement, there are a number of important reasons to collect data on a consistent basis.

- *Provide baseline information prior to starting a behavior program*. Before beginning any behavior program, it is recommended that data be collected on the person's target behaviors. Baseline data provides the behavior programmer and staff with a clear picture of the frequency of maladaptive behaviors being exhibited by the person. This information bears directly upon the design of the treatment plan. For example, if, after baseline data analysis, it is determined that the target behavior rate is extremely high, then one would not choose to implement a DRO program, which is suited for low-rate behaviors.
- *Method for judging the ongoing effectiveness of the behavior program*. Systematic collection and graphing of data is important in tracking the progress of a treatment plan. Trends in data can be analyzed to support any changes necessary to the initial program. Modifications to the program should be data-driven and not based on anecdotal staff reports alone.
- *Feedback to family, staff, payers, and patient*. Behavior data provide important information to those responsible for the patient's well being and/or funding. People typically respond more favorably to observationally recorded data of behavior rather than statements such as "They are behaving better." Graphs, based on collected data, help the patient, staff, and others visualize and understand the impact of the behavioral intervention plan. Graphs can also assist the patient in developing self-monitoring skills.
- *Valuable information for research and program development*. If the person is in a school or rehabilitation program, systematic collection of behavior data assists those responsible for clinical research, conference presentations, preparation of professional manuscripts, and program development. These activities require the support of reliably collected data.

Data collection

There are many methods for collecting data. The three most common and practical methods are event recording, interval recording, and time sample recording. These three data collection methods are known as direct observational recordings (Table 25.3).

EVENT RECORDING

Event recording (Figure 25.3) is probably the easiest direct observational recording system. The only requirement is to mark on a piece of paper each time a specific target behavior occurs. Hand-held devices, such as golf counters, can be used to make counting easier for high-frequency behaviors. The drawback to event recording is that it can be difficult to judge when one occurrence of a behavior ends and another occurrence begins. In tallying angry language, for example, if a person is yelling for several minutes, it would be difficult to judge how many instances of angry language actually occurred. The person recording would have to decide whether to count the entire period as one event or try to tally each statement as a separate occurrence. In addition, high-frequency and long-duration behaviors are more difficult to count because of the amount of attention required. Event recording requires constant observation of the patient so that all occurrences of the target behavior are recorded, thus making it one of the most time-consuming of the data collection procedures.

INTERVAL RECORDING

Interval recording (Figure 25.4) eliminates the task of judging the beginning and ending of behavioral episodes and tallying high-frequency or long-duration behaviors. Instead, interval recording divides the therapy session (or observation period) into equal time intervals (e.g., 15-minute periods) and requires the person recording to mark whether or not the target behavior occurred during each interval. It does not matter how many times the behavior occurred during the interval, only that it occurred at least once. Interval recording requires choosing an appropriate interval size. Time intervals should approximate the frequency rate of the behavior. High-rate behaviors require short time intervals (e.g., 5 minutes), and low-rate behaviors need long time intervals (e.g., 15 minutes). For example,

Table 25.3 Direct observational data collection methods

Method	Definition	Considerations
Event recording	Tally *each* occurrence of target behavior	Requires constant observation. Difficult to judge beginning and end of behavior.
Interval recording	Record each occurrence or nonoccurrence of target behavior *during* each interval	Requires constant observation. Results in approximations of behavior duration and frequency.
Time sample recording	Record occurrence or nonoccurrence of target behavior at the *end* of each interval	Broad approximation of behavior duration and frequency.

Client name: **John Williams** Date: **4-14-03** Time: **1–2 pm**

Therapist name: **Mary Smith** Therapy: **OT**

Instructions: Tally the *number of occurrences* of each target behavior.

Target behaviors	Tallies	Total
1. Physical aggression Definition–attempting to and/or actual striking of an individual with an object or body part.	I	**2**
2. Angry language Definition–cursing, threats, or any hostile language delivered with increased volume.	IIIII	**5**
3. Property destruction Definition–attempting to and/or actual damaging of property.	I	**1**
4. Refusal Definition–not starting, interrupting, or stopping therapy or instructions >60 seconds.	IIIIIII	**7**
5. Escaping Definition–attempting to and/or leaving the place of required activity.	III	**3**

Figure 25.3 Example of an event recording sheet.

if a person uses angry language approximately once every 10 minutes, an observation interval of 10 or 15 minutes would capture most of the variability in the behavior. If the interval size is too long, the rate of behavior may change and not be reflected in a measurement of percentage of interval change. When the intervals are extremely short (e.g., 30 seconds), every other interval should be used for marking the data sheet. This achieves greater accuracy because the observer does not miss occurrences of behavior while attending to the recording sheet. If several target behaviors are being tracked simultaneously, the use of behavioral codes is recommended to simplify the procedure. At the end of each interval, the person recording marks the behavioral code (e.g., PA = physical aggression) for those behaviors that occurred during the interval. As in event recording, interval recording requires the undivided attention of the person recording. It is necessary to track both interval time and occurrence of target behaviors.

TIME SAMPLE RECORDING

The last data collection method to be covered is time sample recording (Figure 25.5). Time sample recording is similar to interval recording except that it does not require constant attention by the person recording. Behavior is only periodically sampled. A therapy session (or observation period) can be divided into equal or variable (random) periods at the end of which (during a brief time sample) the person recording marks the occurrence or nonoccurrence of the target behavior. The advantage of this method is that the person recording does not have to continuously monitor the patient's behavior, and it is minimally intrusive on any activities, which also makes it ideally suited for monitoring high-frequency behaviors. It does require a device, such as a timer, to signal the end of each time period. The disadvantage is that time sample recording results in an even broader approximation of behavior frequency than does interval recording.

Client: **John Williams**	Day: **Monday**	Date: **4/14/03**

Instructions: *Every 15 minutes you are to mark any target behaviors, and level of cooperation, listed below that occurred during that period by circling the letter corresponding to the behavior. The interval begins at the listed time (e.g., mark in the 2:00 period behaviors seen from 2:00 to 2:15). Note any observations and comments in the space provided.*

Target behaviors: PA = physical aggression, AL = angry language, PD = property destruction, R = refusal to work, E = Exiting

Cooperation: None = no cooperation (with behavior), Part = partial cooperation (with behavior), Full = full cooperation (no behavior)

Therapy SP	9:00 a.m.	9:15 a.m.	9:30 a.m.	9:45 a.m.
Target behaviors >	PA AL PD R E	PA AL PD R E	PA AL PD R E	PA AL PD R E
Cooperation >	None Part Full	None Part Full	None Part Full	None Part Full
Comments/other >				
Therapy OT	10:00 a.m.	10:15 a.m.	10:30 a.m.	10:45 a.m.
Target behaviors >	PA AL PD R E	PA AL PD R E	PA AL PD R E	PA AL PD R E
Cooperation >	None Part Full	None Part Full	None Part Full	None Part Full
Comments/other >				
Therapy ED	11:00 a.m.	11:15 a.m.	11:30 a.m.	11:45 a.m.
Target behaviors >	PA AL PD R E	PA AL PD R E	PA AL PD R E	PA AL PD R E
Cooperation >	None Part Full	None Part Full	None Part Full	None Part Full
Comments/other >				
Therapy PT	1:00 p.m.	1:15 p.m.	1:30 p.m.	1:45 p.m.
Target behaviors >	PA AL PD R E	PA AL PD R E	PA AL PD R E	PA AL PD R E
Cooperation >	None Part Full	None Part Full	None Part Full	None Part Full
Comments/other >				
Therapy RT	2:00 p.m.	2:15 p.m.	2:30 p.m.	2:45 p.m.
Target behaviors >	PA AL PD R E	PA AL PD R E	PA AL PD R E	PA AL PD R E
Cooperation >	None Part Full	None Part Full	None Part Full	None Part Full
Comments/other >				
Therapy SP	3:00 p.m.	3:15 p.m.	3:30 p.m.	3:45 p.m.
Target behaviors >	PA AL PD R E	PA AL PD R E	PA AL PD R E	PA AL PD R E
Cooperation >	None Part Full	None Part Full	None Part Full	None Part Full
Comments/other >				

Figure 25.4 Example of an interval recording sheet.

DATA MANAGEMENT

The field of data management technology is changing very quickly, so it requires frequent investigation to stay current. By staying up to date on these technologies, one can continue to ease the burden of data collection, summarization, and visual representation. A number of software programs are available that are well-suited to managing and graphing behavior data, including spreadsheet programs, scanning software, and mobile device applications. Spreadsheet programs, such as Excel*, are very useful for this purpose and typically include organized storing, calculating, and graphing capabilities. Figure 25.6 is an example of a computer summary sheet covering 1 week of interval data. It includes columns for the date, day, each target behavior (e.g., PA = physical aggression), and the total number of intervals recorded. All that is required is to write simple formulas for each of the calculations and design a master form that can be retrieved for each new patient.

An option, especially for high-volume data collection, is electronic forms. Most of us are familiar with survey forms and questionnaires that we receive in the mail. After we fill them out, we either fax or mail the completed forms to the

* Microsoft Excel 2015, Copyright 2015 Microsoft Corporation.

Client Name: **John Williams** Date: **4-14-03** Time: **2–3 pm**

Therapist Name: **Mary Smith** Therapy: **OT**

Instructions: At the times listed in the left column, observe the client for 30 seconds then put an X under *Yes* if the target behavior occurred, or under *No* if the target behavior did not occur.

Target behavior	Definition
Angry language	Cursing, threats, yelling, or any hostile language delivered with increased volume.

Time	Yes	No	Time	Yes	No
9:00	X		9:32		X
9:03		X	9:35	X	
9:10		X	9:40	X	
9:15	X		9:47		X
9:23		X	9:51		X
9:25		X	9:56	X	

Data calculation:

Total Yes's = 5 Total Yes's/ total samples = 5/12

Total No's = 7

Total samples = 12 = 42% of time samples

Figure 25.5 Example of a time sample recording sheet.

John Williams

Week 1	PA	AL	PD	R	E	T
4/10	1	5	0	2	1	24
4/11	0	2	0	1	0	20
4/12	3	5	1	3	1	24
4/13	1	1	0	0	0	20
4/14	2	4	1	2	1	24
Total	7	17	2	8	3	112
Percentage	6.25	15.18	1.79	7.14	2.68	

Figure 25.6 Example of a computer summary data sheet. PA, physical aggression; AL, angry language; PD, property destruction; R, refusals; E, exiting; T, total intervals.

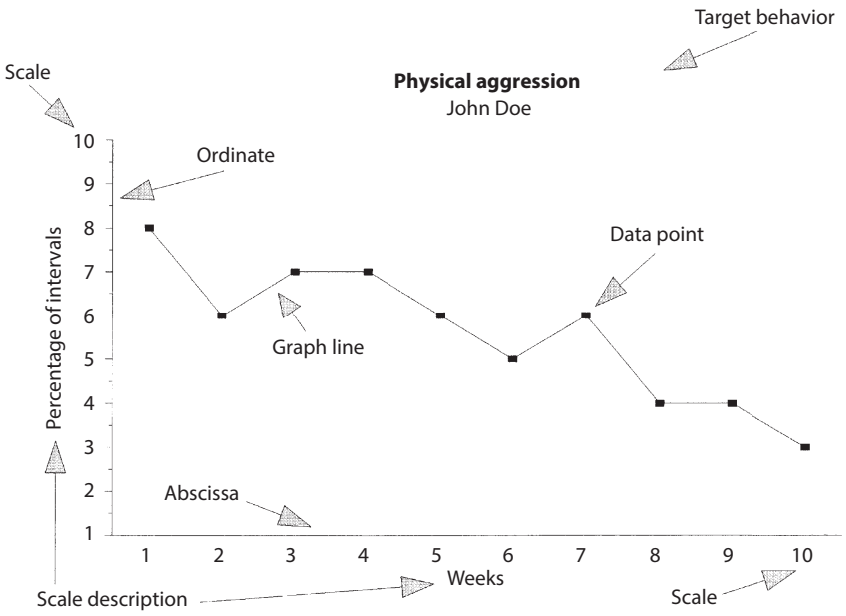

Figure 25.7 Components of a graph.

survey company. Behavior data can be collected in the same fashion. Behavior data sheets can be created in an available program, such as Scantools,* which can scan and organize high-volume behavior data.

The use of mobile devices, for example tablets, is becoming an increasingly more common means of data collection in the health care field. This technology offers many advantages, such as ease of use, automatic data organization, audio reminders and alerts, graphing capability, video capture, etc. Two currently popular applications are Behavior Tracker Pro† and ABC Data Pro.‡

Graphing

Due to its single-case structure, behavior analysis does not lend itself to statistical procedures to judge the effectiveness of treatment interventions. Graphs are the traditional means of accomplishing this task. They provide an overall visual impression of behavior that is easy for staff, families, patients, and others to understand. As it is common for behavior problems to accelerate before decreasing after the introduction of the treatment intervention, graphs are an easy way to track learning curves. Graphs can be produced by hand, with one of the numerous commercially available computer graphics programs, or with a spreadsheet program, such as Excel.

There are two fundamental concepts to remember when graphing: first, what information goes with the vertical line (ordinate or y-axis) of the graph and, second, what information goes with the horizontal line (abscissa or x-axis) of the graph. Figure 25.7 labels all the basic components of a graph.

For event-recorded data, the ordinate indicates the number of occurrences of the target behavior (e.g., physical aggression), and the abscissa indicates the time across which the behavior was recorded (e.g., days, weeks). For example, if one were graphing the number of occurrences of physical aggression on a weekly basis, the graph would look something like Figure 25.8.

In addition, choose the maximum value for the ordinate scale based on a number that is slightly higher than the highest frequency that has occurred with the person. For example, if the highest number of occurrences of physical aggression in a week was four, then choose five as your maximum value for the ordinate scale.

For interval or time sample recording, the ordinate of the graph indicates the percentage of intervals (or time samples) in which the target behavior has occurred. The abscissa of the graph represents the time period during which the behavior was recorded. For example, if one were graphing the percentage of intervals for physical aggression on a weekly basis, the graph would look something like Figure 25.9.

Choose the maximum percentage for the ordinate scale based on a slightly higher percentage than the maximum that has occurred with the person. For example, if the highest percentage of intervals with physical aggression in a week was 20%, then choose 25% as your maximum value for the ordinate scale.

Interpreting graphs can sometimes be very difficult. Behavior that is either highly variable or changes very little can make analysis a challenging proposition. One can look for a general trend or slope, or one can begin grouping data and comparing means (averages) to help detect changes in behavior.

* Scantron Corporation, Copyright 2015.

† Data Makes the Difference, LLC, Copyright 2015.

‡ CBTAonline, Copyright 2015.

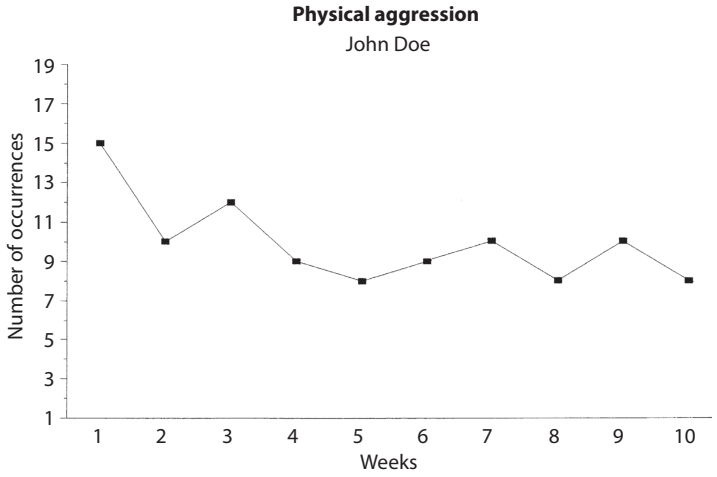

Figure 25.8 Example of an event graph.

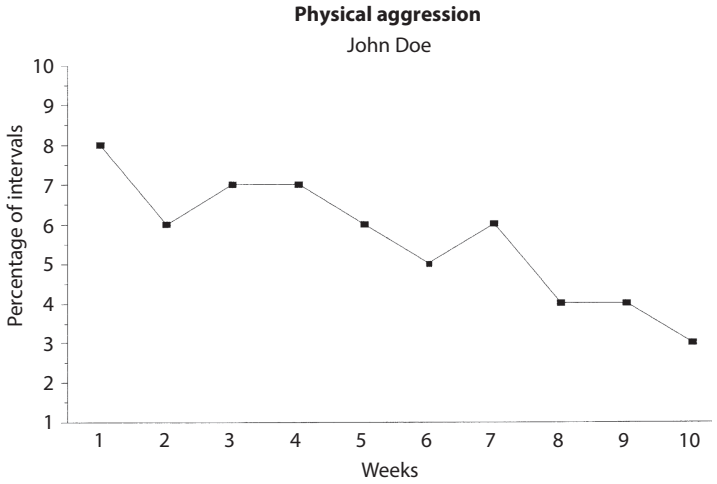

Figure 25.9 Example of an interval or time sample graph.

A graphing technique we have found to be extremely useful in situations in which interpretation is difficult is called trend graphing. This graph is tedious to complete by hand, but most spreadsheet programs now have the ability to calculate a "line of best fit" graph. If we take a behavior (e.g., physical aggression) and create a trend graph, it will show us the future projected change of physical aggression based upon the current observed rate of change. Figure 25.10 is an example of a trend graph. It clarifies the effect of the treatment and indicates when a target behavior might be expected to reach a projected goal. Of course, there are numerous variables that can have an impact on goal attainment, so care must be taken when interpreting trend graphing.

CRISIS PREVENTION AND INTERVENTION

Assaultive behavior, such as physical aggression, is common in the field of TBI rehabilitation.[61] All of the planning and programming described in the previous sections cannot always prevent or predict the occurrence of assaultive behavior by a patient. In some cases, behavioral programming may even elicit aggression when it exerts control over sensitive aspects of a patient's environment. Assaultive situations can be a frightening experience. People can be combative during the acute phase of recovery as they reorient themselves to the world around them and during post-acute rehabilitation (i.e., when a person has reached medical stability) as they develop awareness of functional deficits. Severe behavior is a reality of the rehabilitation process, and staff can learn to take measures, when possible, to prevent its occurrence. However, if a crisis situation does occur, staff should also be equipped with techniques to de-escalate the patient and decrease the likelihood of injury to the patient and others.

This section covers some basic models of the assault cycle, common reasons for assaultive episodes, techniques for preventing the development of crisis situations, and useful interventions if a crisis cannot be prevented. However, this chapter is not a replacement for a certified course in

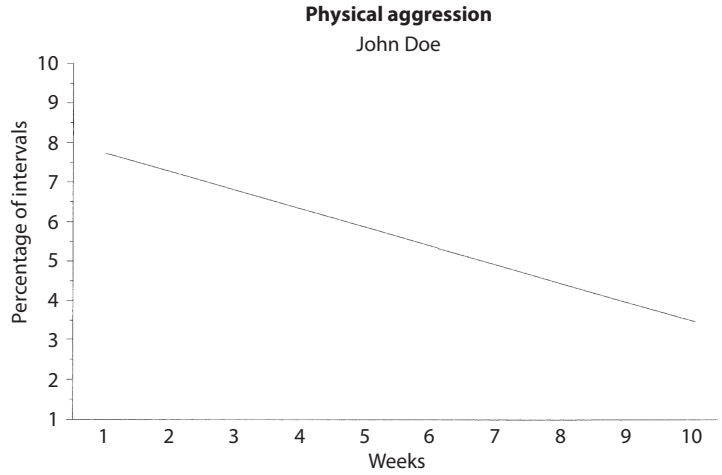

Figure 25.10 Example of a trend graph.

crisis intervention or management of assaultive behavior. There are a number of training programs available to train staff directly or to certify staff members as instructors. We highly recommend that all facilities, schools, or families that work with people with TBI with behavior problems incorporate this training as standard practice. The content, structure, and training methodology of these courses, including the practice of self-defense and restraint techniques, is an effective means of comprehensively equipping a person to safely handle assaultive situations.

Models of assault

Paul Smith,[258] founder of Professional Assault Crisis Training and Certification (Pro-ACT),®,* has proposed two categories and seven models of assaultive behavior. The first category is identification models, and it includes the stress model, communication model, environmental model, developmental model, and basic needs model. The second category is response models, which includes the common knowledge model and legal model. We only concern ourselves here with five of the models. The developmental model and basic needs model are not as clearly related to the field of TBI rehabilitation.

IDENTIFICATION MODEL

Stress model

The stress model views assaultive behavior as a reaction to extreme stress. The rehabilitation process, as we know, is an extremely stressful situation for a person. When a patient perceives a threat to his well being (e.g., daily confrontation of deficits), he can either fight or flee from the situation. In TBI rehabilitation, we see both of these responses. Some patients try to escape the stress of their condition by either escaping or avoiding therapy. Others become combative when stressed. Each patient has specific responses to stress, which can be detected and recognized as predictable patterns. A common tool for visualizing these response patterns is "The Assault Cycle" graph (Figure 25.11). It is divided into five separate phases. They are 1) triggering event, 2) escalation, 3) crisis, 4) recovery, and 5) postcrisis depression.

The triggering event is any stimuli or event that exceeds the patient's tolerance for stress (e.g., demands for compliance, being touched, etc.). This begins the assault cycle. Any prevention techniques (e.g., arranging of environment, level of demands, etc.) would have to occur before the triggering event. The escalation stage is characterized by increasing levels of agitation or changes in the normal (i.e., baseline) behavior of the patient. De-escalation techniques are used during this phase to try to help the patient return to a baseline level of behavioral activity. The sooner de-escalation techniques are used during this stage, the less likely more restrictive measures will have to be implemented. The crisis stage is characterized by the patient's physically acting out. At this point, de-escalation techniques have failed, and physical intervention may be necessary. During the recovery phase, the patient's level of activity is decreasing. Once the person regains self-control, decrease any external control that may have been introduced. The last stage, postcrisis depression, is characterized by activity that falls below baseline levels. The patient may require a short period of rest or less active tasks until recovery occurs.

Communication model

The communication model focuses on the balance of communication between the therapist and patient. On one end of the spectrum is "withdrawal" and on the other end "assault." Smith[258] believes that the best means for achieving a "balance" that decreases the chances of triggering an assaultive cycle is with assertive communication. Smith[258] states that the communication model takes into account patient manipulation and intimidation. When staff members respond with either intimidating aggressiveness or

* Registered Trademark of Professional Assault Crisis Training and Certification, San Clemente, CA, 2004.

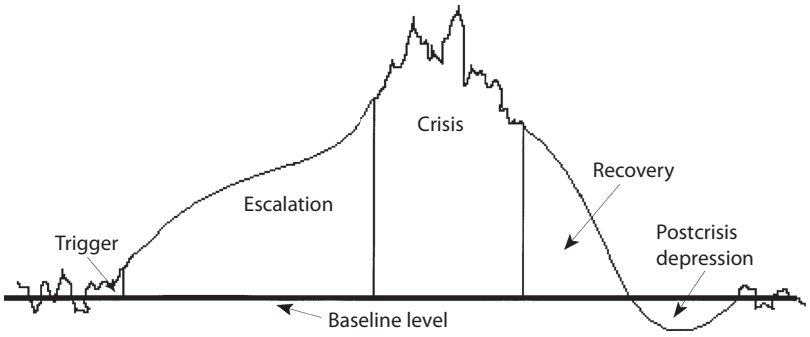

Figure 25.11 The Assault Cycle. (From Smith, P., Professional Assault Response Training Workshop Syllabus, 1983. With permission.)

submissive nurturing, they contribute to an imbalance of communication and increase the opportunity for an assaultive situation. Smith[258] emphasizes that, "by using assertive communication, employees (or patients) reduce the chance that an assault will occur." (p. 13)

Environmental model

Smith[258] describes the environmental model from the perspective that assaultive behavior is, for the most part, a product of the circumstances in which it occurs. This is the model that most closely fits the fundamental philosophy of behavior analysis. Although Smith does not discuss consequences to behavior as part of his model, he does emphasize the role of antecedents and setting events in triggering or setting the stage for assaultive behavior. Such things as weather conditions, level of sound, crowding, and scheduling of activities are given as examples of events that can "predispose people to assaultive behavior." The important point to make concerning the environmental model is that the staff is in control of most environmental antecedents to behavior. Schedules, noise level, tone of voice, etc., are usually under the control of the staff. Staff can take advantage of this opportunity to prevent "trigger events" and minimize assaultive behavior.

RESPONSE MODELS

Common knowledge model

Smith[258] believes that the underlying reasons as to why people attempt to injure one another are relatively simple and that one can apply intervention techniques to effectively respond to these events. He states that assaultive incidents can be reduced to four common motives: fear, frustration, manipulation, and intimidation.

When people are afraid or feel that their safety is threatened, their behavior may escalate to physical aggression as a means of defending themselves. To reduce fear, staff can respond to the patient with a relaxed posture; use slow and natural gestures; keep a safe distance from the patient; stand off to the side; position oneself below the patient's eye level; use a firm, yet reassuring, voice; stay logical; and encourage calm reflection.

When a patient's behavior escalates as a result of frustration, staff members need to follow different guidelines than those used with a fearful patient. Staff should demonstrate control with a more commanding posture; use forceful gestures, such as pointing; stay directly in front of the person but just out of reach; keep the tone of voice quiet, yet forceful and confident; and repeat commands.

If a patient is escalating behaviorally as a means of manipulation, a role of "detachment" is the technique recommended by Smith.[258] This method involves maintaining a closed, yet relaxed, posture; mild gestures of disapproval (e.g., finger tapping); positioning far enough away from the patient to show noninvolvement; turning slightly away from the patient; using a detached, slightly "bored" tone of voice; and quiet, repetitive commands.

If the patient is attempting to intimidate through escalated behavior, the technique Smith[258] advises is "identifying consequences." The basic premise is that clear communication of the consequences of an assaultive act will reduce the probability that the episode will occur. Staff should be poised and ready to react (without giving the impression of fear); keep gestures to a minimum; position oneself for protection (e.g., behind a chair or desk); maintain a monotone, emotionless tone of voice; and give clear and direct statements of consequences.

Legal model

Assaultive behavior can be separated into legal categories. They are 1) simple assault, 2) assault and battery, and 3) aggravated assault. The staff can legally protect itself against these varying degrees of assault but is limited to using only "reasonable force." As Smith[258] states, "A reasonable amount of force is just enough for effective self-protection …" (p. 11). For example, with simple assault (i.e., threatening gestures or speech), communication techniques would be the maximum force that could be legally applied. With assault and battery (i.e., use of physical force and threats), evasive self-defense would probably be the maximum reasonable force allowed. If aggravated assault (i.e., attempt to cause serious bodily harm) occurs, a controlling self-defense (i.e., restraint) and physical intervention would be reasonable. The use of physical techniques for self-defense and other interventions requires intensive training. Unless a staff member has completed this training, he should have limited contact with patients exhibiting severe behavior disorders.

General techniques and methods

There are many techniques for preventing a crisis situation or intervening once it has started. We have covered many of those methods in the previous section. Smith's[258] recommendations regarding body posture, tone of voice, content of speech, and use of gestures are invaluable aids to dealing effectively with a crisis episode. There are other techniques that can be added to this list.

To help prevent a crisis situation from being "triggered," review the guidelines outlined in the "General management guidelines" section of this chapter. These include 1) increasing rest time for the patient, 2) keeping the environment simple, 3) keeping instructions simple, 4) giving feedback and setting goals, 5) staying calm and redirecting the patient to task, 6) providing choices, 7) decreasing chances of task failure, 8) varying the type of activities, 9) over-planning, and 10) utilizing task-analysis procedures. If one can implement these environmental controls and combine them with sensitivity to patterns of interaction and sharpened observational skills, most assaultive events can be prevented. For those that are unavoidable, intervention techniques for de-escalating the patient must be employed.

Once the escalation phase of an assault cycle has begun, measures by staff change from one of prevention to one of intervention. The intervention techniques used during the escalation stage are an attempt to de-escalate the patient before the cycle reaches the crisis stage. The earlier the intervention, the less restrictive the measures will need to be to control the situation. If the patient progresses to the crisis stage, de-escalation techniques will not be useful and may, in fact, prolong the crisis. Physical intervention by staff, unfortunately, becomes likely.

Some of the most effective de-escalation techniques staff can utilize are active listening, orientation, setting limits, redirection, withdrawal of attention, and contracting.

- *Active listening.* A technique incorporating a variety of listening skills.[259] Active listening begins on a "nonverbal" basis. The staff member should make eye contact with the patient, maintain a relaxed posture that shows interest, and use natural gestures. Once this nonverbal basis has been established, verbal statements can be utilized. These consist of paraphrasing, clarifying, and perception checking. Paraphrasing is a method of restating the patient's message in fewer words. Its purpose is to indicate to the patient that you are trying to understand his message. Clarifying focuses on the more abstract messages from the patient. The staff member admits confusion about a statement and tries a restatement or asks for clarification—for example, "I'm confused; is what you are saying …?" Perception checking involves asking the patient for verification of your perception. For example, "You seem to be very mad at me. Is that correct?"
- *Orientation*. Memory deficits are one of the most common consequences of a TBI. People can experience periods of severe disorientation. Disorientation has been found to be a key factor in the severe behavior of people with TBI. Orienting a patient to the time, to his location, and to whom he is with can sometimes help to de-escalate a patient. It helps the patient feel less threatened by the environment when he can understand where he is and why he is there.
- *Setting limits*. As stated earlier, setting limits can be a useful technique. This is especially true for patients who are trying to intimidate staff by threatening severe behavior. Although these can be frightening experiences, escalation can be curtailed if the staff member remains calm and confident and outlines the consequences of the threatened behavior. For example, "If you throw that chair at me, you will be restrained by four other staff members until you are calm."
- *Redirection*. Also known as topic dispersal, this is useful when a patient is in the early stages of escalation. Staying calm and redirecting a patient to another task or activity can interrupt the escalation phase and refocus the patient on something else. It also decreases the opportunity for inadvertently reinforcing the patient with attention that may be the behavior problem's maintaining reinforcer.
- *Withdrawal of attention*. This technique is the opposite of active listening. Whereas active listening provides undivided attention to the patient during escalation, withdrawal of attention discontinues any attention during escalated behavior. Withdrawal of attention is usually more effective with "manipulative" types of behavior. Patients exhibiting this type of behavior thrive on attention from others. Withdrawing attention for brief periods of time when they begin to escalate helps establish a relationship between "attention" and cooperative, calm behavior.
- *Contracting.* Like other de-escalation techniques, this is a skill that takes some practice. The reason, however, is that contracting has the potential for being misused. If used incorrectly, it becomes a method of "buying" good behavior that may lead to further behavior problems from the patient. For example, if a patient is escalated over completing an unpleasant task and you "contract" with him that he does not have to finish the task if he calms down, you have set yourself up for future problems when the patient does not want to complete a task. You may have reinforced the escalated behavior. A more constructive response may be to tell the patient that he can switch to another task for the moment and finish the difficult task later in that session. This teaches the patient that he can let you know when he has reached his limit of frustration with an activity and would like to work on something else for a while.

The models of assault, as outlined by Smith,[258] provide us with a structure in which to view crisis episodes. Techniques for prevention should be the first line of defense in dealing with severe behavior problems. Behavior treatment plans

should always include instructions for controlling antecedents and setting events to help prevent problem behaviors from occurring. If they do occur, the treatment plan outlines the consequences to the behavior and provides procedures for staff to follow. All crisis situations, however, cannot be predicted or prevented by a behavior program. This is why it is important for staff to be trained in techniques and methods of crisis intervention. We hope the techniques described in this section, although not a substitute for direct training, will at least assist staff and family members with basic approaches to crisis intervention.

Recommended Training

Pro-ACT, Inc.
154-A W. Foothill Blvd.
Suite 316
Upland, CA 91786
(909) 758-0322
info@parttraining.com
parttraining.com

Crisis Prevention Institute, Inc. (CPI)
10850 W. Park Pl.
Suite 600
Milwaukee, WI 53224
(888) 426-2184
info@crisisprevention.com
crisisprevention.com

STAFF AND FAMILY TRAINING

A fundamental component of the implementation of a sound behavioral treatment plan is staff training. To be successful in treating people with TBI with behavioral difficulties, rehabilitation facilities must be committed to providing adequate staff training and support. This commitment is not only one of allocating the time and financial resources for training, but also of providing philosophical support of behavioral principles, use of its techniques, and sufficient staffing levels to effectively carry out behavior programs. Without this foundation, it would be very difficult for a facility to realize the full benefit of behavioral programming. These issues aside, training consists of the following steps:

- *Basic principles*. Training must begin with an understanding of basic behavioral principles. Staff should be able to identify environmental influences (antecedents and setting events) and responses (consequences) that help to maintain target behaviors. It is especially important for staff and families to understand the importance of consistency in implementing treatment plans and in responding to patient behavior.
- *Data collection*. Staff members require training to enable them to accurately observe patient behavior and reliably record data. This can include training to criteria. For example, staff can observe patient behavior on video tape and fill out data sheets until they are within 90% agreement of pre-established scoring.
- *Behavior procedures*. It is important for staff and families to understand the structure of behavior treatment design, for example, the differences between accelerative programs (e.g., positive programming), decelerative programs (e.g., DRO), and complex programs (e.g., token economy). Staff members are better able to consistently follow programs that they understand.
- *Ethical issues*. It is recommended that staff and families be informed of current ethical issues and guidelines regarding the use of behavior programs. Applied behavior analysis can be a powerful and controversial intervention for behavioral change. The procedures must be implemented with great care, understanding, and sensitivity.
- *Environmental validity and generalization*. Staff and families need to understand the concept of environmental validity (the teaching of skills at the proper time and in a natural setting) and generalization (the transfer of skills from one setting to another). Skills are not useful if they cannot be performed in the correct context or cannot be transferred from a clinical setting to the home and community. For example, being able to dress in a clinic treatment room at 11 a.m. is not the same as being able to dress at 7 a.m. in your own bedroom.
- *Team approach*. Training should emphasize the importance of a team approach to applied behavior analysis. Assisting one another in crisis situations or helping when a patient or staff member is not "having a good day" are just a couple of situations that illustrate the need for staff to act as a team. Staff members are more confident about implementing behavior programs when they know that others are there to help if the circumstances warrant it.
- *Management of assaultive behavior*. Even the most effective behavior programs may not always prevent a crisis situation. Several courses provide training in management of aggressive behavior and crisis intervention. They typically include methods of observation, de-escalation, self-defense, and physical restraint. This training, in our experience, affords one of the best means for instilling confidence in staff to effectively work with behaviorally difficult patients. It provides for a systematic approach to aggression and a structure in which all behavioral interactions and interventions can be gauged. These courses tend to emphasize early intervention in the patient's "assault cycle" before it reaches a crisis stage that requires physical intervention. This training also provides a useful means for ensuring adherence to the legal requirements of balancing the restraint of patients and self-defense.
- *Behavior staffings*. Staff members require a forum to openly address and discuss current behavioral issues. Staff can, at times, be hesitant to discuss patient behavior, so they may require assertive questioning by the facilitator to draw out details of behavioral episodes and the surrounding factors that might be influencing the behavior. Frequent behavior staffings are also necessary for keeping abreast of the latest behavioral concerns as well as providing an excellent venue for continuing staff education on behavior methodology.

- *Family training*. Many patients continue to have behavior problems that persist after being discharged from a facility. Those people who will play a significant role in the patient's life after rehabilitation will need training in the proper use of behavior analysis and access to behavior specialists for ongoing support. Facilities can provide families with the same training as their staff. Family members can practice behavior procedures (with the patient) under the guidance of the facility. Without this training, behavioral stability after discharge from a facility is less likely to be maintained.

PUTTING IT ALL TOGETHER

This chapter has described the basic components of effective behavior program design. However, each component does not stand alone. All of the steps are integrated and must be systematically completed in order to reach the desired behavioral outcome.

- *Perform behavioral diagnostics*. First, a thorough assessment must be performed. This consists of reviewing historical information about the patient that helps the behavior programmer understand how the patient may respond to rehabilitation and what he or she expects to gain from treatment. It involves evaluating the patient's current functional skills and analyzing clinical test results that can dictate the type of behavioral procedure that is implemented. Most importantly, a thorough behavioral assessment includes a functional analysis that identifies the function served by each target behavior.
- *Identify potential conditions maintaining the behavior*. The result of behavioral diagnostics should be the identification of conditions that might be supporting the target behavior. Is there an antecedent or setting event to the behavior? Are there responses to the behavior that are reinforcing? What function might the behavior be serving? The three parts of a functional analysis are 1) identification of the target behavior and its surrounding events, 2) predicting the factors that control the behavior, and 3) testing of the behavioral hypothesis by manipulating those factors.
- *Collect baseline data*. Once the assessment is complete, the target behavior defined, and the maintaining conditions identified, baseline data can be collected. Baseline data will provide valuable information concerning the frequency and duration of the target behavior and a means for judging the effectiveness of the treatment procedure. The behavior programmer can choose an event, interval, or time sample recording method based on the characteristics of the target behavior. Event recording is better suited to discrete behaviors (i.e., those with a clearly defined beginning and end). Time sample recording is more appropriate for high-rate behaviors that are ill-suited to constant observation, and interval recording works for general-purpose data collection.
- *Design and implement treatment procedures*. After baseline data has been collected, a treatment plan can be designed and implemented. The behavior program should include short- and long-term goals, rationale, clear operational definitions of the target behavior, a list of any materials needed, contraindications, a description of the data collection system, and procedures for staff to follow. Procedures can be accelerative (designed to increase the target behavior), decelerative (designed to decrease the target behavior), or complex (having characteristics of both accelerative and decelerative programs). Effective behavioral programming may even require combining more than one of these procedures simultaneously.
- *Continue data collection*. Once the treatment plan has started, data collection should continue as a means of monitoring the progress of the patient. Data recording sheets should be completed on a daily basis in as many environments and conditions as possible. Systematic data collection allows the programmer, staff, patient, family, and others to be kept abreast of the patient's progress. People typically respond more favorably to observationally recorded data of behavior than statements such as "They are behaving better."
- *Graph and analyze behavior data*. Behavior data should be routinely summarized and graphed. Graphing is one of the best means for analyzing the effect of a treatment plan. It provides an overall visual impression of behavior that is easy to understand and, also, an effective way of tracking learning curves. The behavior programmer can then base any modifications to the treatment plan on more objective data rather than anecdotal reports.
- *Modify treatment procedures*. Treatment procedures should be altered only when there is sufficient evidence in the data to indicate a failure in the procedure's effectiveness or when the data indicates a need for a transition to a less structured approach. This can happen when the original behavior problem has been resolved. In this situation, the use of trend graphing can be useful. Trend graphs show the future projected change in a behavior based on the current observed rate of change.
- *Plan for generalization and maintenance of changed behavior*. Treatment plans are not successful if a behavioral change is not generalized to other environments and conditions and maintained over time. As treatment and recovery progress, procedures require modification—for example, thinning a reinforcement schedule or decreasing dependence on prompts. If the patient will be living with others after rehabilitation, training of these individuals in basic principles and treatment procedures is essential for a successful outcome. Long-term maintenance of behavior changes can hinge on the ability of family and friends to continue the treatment plan after a patient has been discharged from a facility.

CONCLUDING REMARKS

As the field of TBI rehabilitation continues to evolve, behavioral treatment procedures are being recognized as an essential component of successful patient outcome. Applied behavior analysis provides the structure and consistent feedback required by people with TBI. Although many facilities understand the concepts of behavior analysis and recognize the need for its implementation, the authors have seen too few facilities actualize this ideal. Usually, this is a result of a division between a behavioral approach on the one hand and a therapeutic approach on the other. Behaviorally-oriented staff focus primarily on the behavior of a patient whereas therapists' main concern is with recovery of lost cognitive and physical skills. Both need to work together, recognizing shared goals and the contribution each makes to the total rehabilitation of the patient. The result of any such division is that behaviorally challenged patients are undertreated, not able to progress to their highest level of independence and, in many cases, placed in a long-term restrictive environment.

Emphasizing positive programming while minimizing aversive procedures is the current mantra of behavior analysis. Legal and ethical concerns related to the use of aversive procedures make these programs increasingly more difficult to implement, which is understandable but, at the same time, can potentially generate unfortunate and impractical consequences. The full spectrum of behavior technology, properly utilized with comprehensive ethical guidelines and monitoring, can maximize treatment efficiency and positive outcome for the patient.

Applied behavior analysis is an essential component in helping people with TBI rebuild their lives. Helping these individuals reintegrate into the home, community, and work settings presents a great challenge to the field of rehabilitation. Behavior analysis provides an effective means of achieving this goal.

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Rehabilitation and management of visual dysfunction following traumatic brain injury

PENELOPE S. SUTER

INTRODUCTION

The two million neurons carrying information from the eyes provide approximately 70% of the sensory input to the brain. Because of this, the visual system gives us enormous leverage to make changes in neurological systems and, with appropriate therapeutic guidance, can often be the keystone of recovery. However, because the visual system is an input and processing system, it is frequently overlooked by rehabilitation teams. Deficits in the visual system are reflected in motor output, gait, balance, speech, and reading. It should not be surprising, then, that vision deficits are frequently unrecognized in the rehabilitation setting as the vision deficits reflected in those output systems are frequently misinterpreted as motor apraxia, motor ataxia, vestibular dysfunction, aphasia, or dyslexia.

This chapter surveys the nonsurgical rehabilitative services available to provide effective treatment of brain-injured patients with visual sequelae. It should be a useful reference for those who deal with these patients in intensive rehabilitative environments as well as for primary care professionals who sometimes find these patients in their care when a rehabilitative hospital or center is not accessible. It may also be useful to both novice and experienced vision care providers working in the area of traumatic brain injury (TBI) rehabilitation.

Many of the therapeutic approaches used with TBI patients were developed for other special-needs vision patient populations. For this reason, much of the information provided here is applicable not only to the TBI patient, but also to other patients who have suffered organic insult to the brain. For the same reason, although they may lack specific experience with TBI patients, vision care professionals who practice other forms of vision therapy will often be able to provide appropriate rehabilitation for TBI patients suffering from visual dysfunction—given a few additional concepts that are specific to the brain-injured population.[1]

PHYSICAL SUBSTRATES OF VISION

The physical substrates of vision are covered in depth in Chapter 9 of this volume, and only a brief overview is given here. Estimates by surface-based mapping in humans demonstrated that approximately one third of the human neocortex is devoted to processing vision.[2] Researchers have described approximately 305 intracortical pathways linking 32 different cortical areas implicated in visual function in the primate; 25 of these are regarded as either predominantly or exclusively involved in visual function, and seven are considered visual-association areas.[3] The one million ganglion cells traveling from each retina represent approximately 70% of all sensory input fibers to the brain. By contrast, the auditory nerve is comprised of approximately 35,000 nerve fibers. Four of the 12 cranial nerves subserve only vision (CN II, CN III, CN IV, and CN VI). Two additional cranial nerves supply sensation from the eyeball (CN V) and motor function to the eyelids (CN VII) along with other structures. Multiple subcortical visual substrates are involved in binocular coordination, visual attention, integrating multimodal stimuli, and perceptual coherence as well as nonvisual light processing involved in diurnal regulation. In addition to these multiple subcortical areas, every lobe of the cortex is involved in visual processing (Reviewed by Kravitz et al.[4,5]; Figures 26.1 and 26.2). The occipital lobe contains the primary visual cortex for initial processing of vision as contour, contrast, and depth. The inferior temporal lobe is involved in object identification, the middle temporal area in motion processing, and the parietal lobe in processing for spatial organization and visual attention.[4,6] The ventral occipital temporal cortex has been implicated in word form recognition, and damage to the vertical occipital fasciculus running from this area to language and reading areas results in pure word blindness.[7] The frontal eye fields and adjacent areas of the frontal and prefrontal lobes are involved in motor planning and initiation of self-directed eye movements as well as visual search.[8] The ventrolateral prefrontal cortex is involved in visual working memory.[9] In addition, simple visual awareness requires interactions between the primary visual cortex, posterior parietal cortex, and the frontal eye fields. Input from the limbic system (especially the cingulate gyrus) may mediate motivational relevance of the external stimulus, guiding sustenance of attentional activation in the visual system.[10] Nonvisual afferent ganglion cells from the retina mediate circadian rhythms at the suprachiasmatic nucleus, which sends messages to the pineal gland for melatonin expression.[11]

Two major processing pathways that are useful for understanding much of the neuroanatomy and neurophysiology of visual rehabilitation beyond primary visual cortex have been established in the literature: the ventral "what is it?" pathway and the dorsal—previously the "where is it?" or "how to do it?" pathway. More recently, Kravitz et al.[4,5] have summarized advances in visual neuroscience and proposed elaborated theories of these two pathways. They present evidence that the ventral pathway is not a simple hierarchical pathway in primates, but a "recurrent occipital–temporal network containing neural representations of object quality both utilized and constrained by at least six distinct cortical and subcortical systems…" that serve behavioral, cognitive, or affective functions linked to object perception.[5] (p. 26) In a separate review paper, Kravitz et al.[4] proposed that the dorsal pathway should be viewed as giving rise to at least three distinct pathways supporting both conscious and nonconscious visuospatial processing: parieto–prefrontal, parieto–premotor, and parieto–medial temporal, which primarily support spatial working memory, visually guided action, and spatial navigation.

Considering the current knowledge of visual neuroanatomy, neurophysiology, and links to visual function, *vision rehabilitation* becomes a sweeping term, which ranges from rehabilitation of the eye and surrounding structures to rehabilitation and management of sensory processing, organization of sensory input from the eye into visual percepts, and use of these percepts to support cognitive or behavioral functions. Visual dysfunction may affect the ability to carry out daily tasks, such as reading, driving, walking, and functioning in the workplace. Diagnosis and rehabilitation of the eye, eyelids, extraocular muscles and surrounding bony structure, eye movement, and eye teaming disorders as well as the higher visual functions, such as visual attention, visual perception, spatial organization, visual memory, and the ability to integrate visual information with other modalities, all fall under the umbrella of visual rehabilitation. Multiple professionals may be involved, and considerable networking or case management provides for the most effective care.

MULTIDISCIPLINARY APPROACH

Two types of eye doctors are frequently required in management of the visual consequences of TBI: the ophthalmologist and the optometrist. In general, their roles may be considered analogous to the computer equivalents of hardware and software repair persons, respectively. The ophthalmologist will often be needed to provide medical or surgical treatment of the hardware, i.e., anatomical and physiological aspects of the visual system, before the optometrist can provide rehabilitation of the software or functional aspects of the visual system.

Ophthalmologists are trained to diagnose and manage damage to the eye and surrounding structures as well as

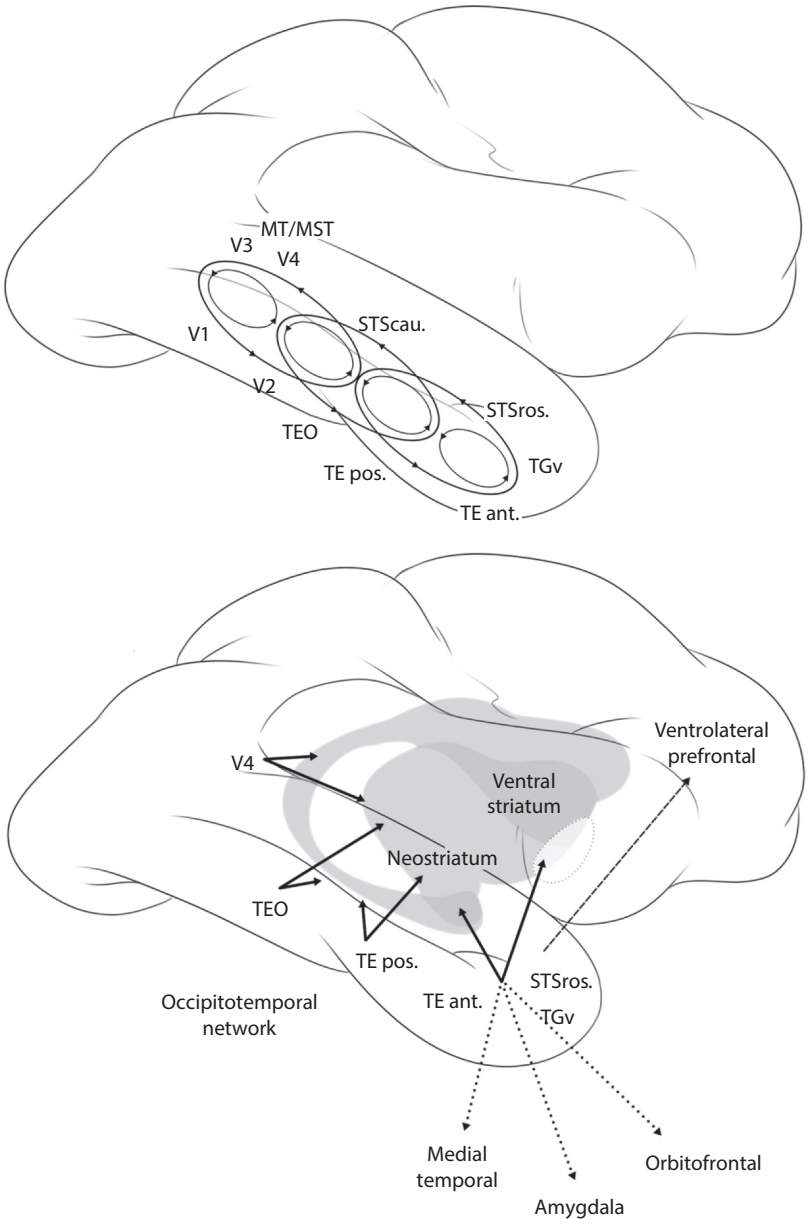

Figure 26.1 A schematic drawing of the "ventral pathway on the lateral surface of the macaque brain. Note the inclusion of visual area V3, the middle temporal (MT)/medial superior temporal (MST) complex, and the superior temporal sulcus (STS), which are typically not included in reference to the ventral pathway. Rather than a simple sequence of projections leading to the anterior inferior temporal cortex, the pathway comprises a series of overlapping recurrent networks of various scales. At the most local level, there are approximately four subnetworks (small black ellipses), each with strong bidirectional connections among its components. Beyond their intrinsic components, these subnetworks are connected to each other via more extended, bidirectional, and nonreciprocal feedback connections that bypass intermediate regions (large black ellipses)…" In the second view, a "…summary of the extrinsic connectivity of the ventral pathway. At least six distinct pathways emanate from the occipitotemporal network. The occipitotemporo–neostriatal pathway originates from every region in the network and supports visually dependent habit formation and skill learning. All other projections originate in the network's rostral portion although not all of these contribute equally to every pathway. One such projection targets the ventral striatum (or nucleus accumbens) and supports the assignment of stimulus valence. Another forms the occipitotemporo–amygdaloid pathway…and supports the processing of emotional stimuli. The occipitotemporo–medial temporal…targets the perirhinal and entorhinal cortices as well as the hippocampus and supports long-term object and object-context memory. Finally, the occipitotemporo–orbitofrontal pathway…and the occipitotemporo–ventrolateral prefrontal pathway…mediate reward processing and object working memory, respectively." Superior temporal sulcus caudal = STScau; rostral STS = STSros; inferior temporal cortex areas = TE and TEO; anterior = ant.; posterior = pos. (Figure adapted from Kravitz, D. J., Saleem, K. S., Baker, C. I., Ungerleider, L. G., and Mishkin, M., The ventral visual pathway: an expanded neural framework for the processing of object quality, *Trends in Cognitive Sciences*, 17, 1, 2013, p. 28.)

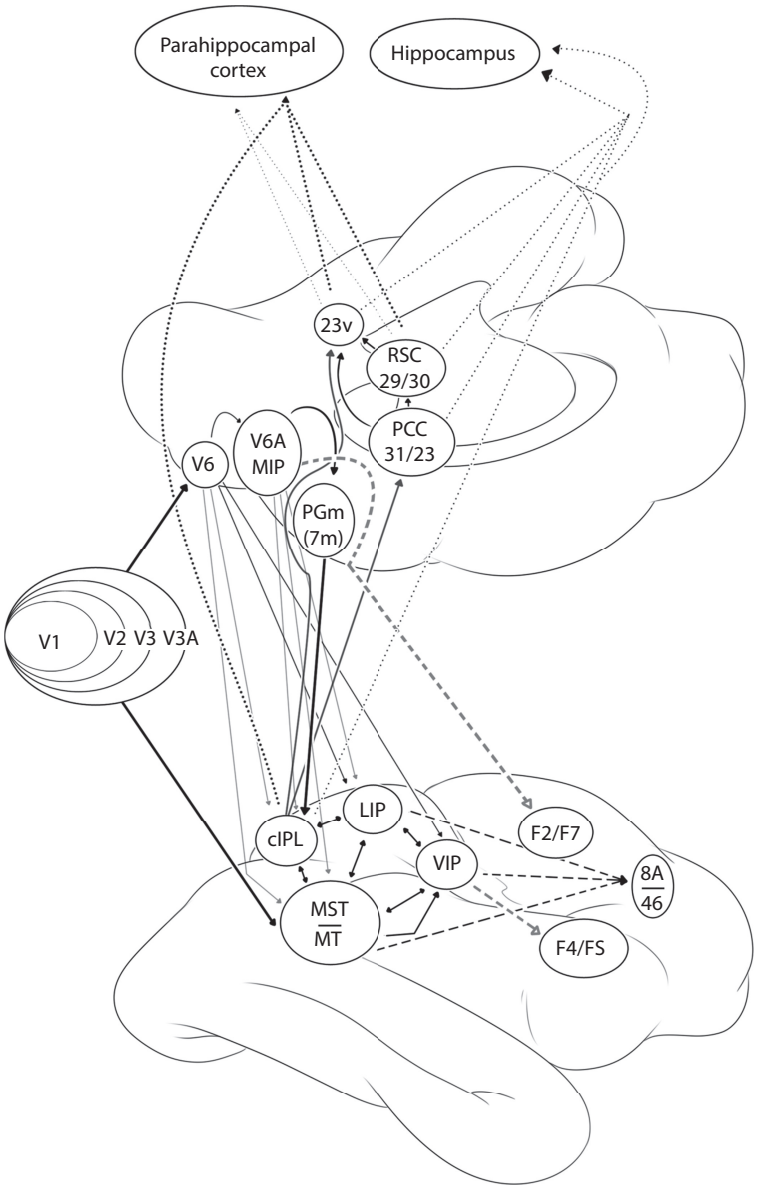

Figure 26.2 Medial and lateral views of rhesus monkey brain showing the anatomy of the occipito–parietal pathways and the three dorsal pathways. V1, also known as the primary visual cortex, is strongly connected with the middle temporal (MT) area through visual areas V2, V3, and V4. V1 also projects through visual areas V2, V3, and V3A to area V6 on the rostral bank of the parieto–occipital sulcus (pos). From area V6, information travels to the parietal lobe through two main channels: the first projecting medially to bimodal (visual and somatosensory) area V6A, medial intraparietal (MIP) area, and the caudal intraparietal sulcus (ips) and the second projecting laterally to the lateral intraparietal area (LIP) and ventral intraparietal area (VIP) and to areas MT and MST in the caudal STS. All posterior parietal areas are strongly connected with each other and with the surface cortex of the inferior parietal lobule (IPL). Feed-forward projections from lower to higher level processing areas are usually reciprocated by feedback projections from higher to lower areas. Connections between areas at the same hierarchical level are indicated by double-ended arrows. The three pathways that emerge from the parietal component of the dorsal stream are indicated by differentially dashed arrows. The *parieto–prefrontal pathway* links areas LIP, VIP, and MT/MST with the frontal eye field and area 46, which subserve eye movement control and spatial working memory, respectively. The *parieto–premotor pathway* links areas V6A and MIP with the dorsal premotor cortex (areas F2 and F7) and also links area VIP with the ventral premotor cortex (areas F4 and F5), which subserve visually guided eye movements and reaching and grasping. The *parieto–medial temporal pathway* "originates in the cIPL and projects to subdivisions of the hippocampus both directly and indirectly via the PCC (areas 31 and 23), retrosplenial cortex (RSC; areas 29 and 30) and the posterior parahippocampal cortex—substrates that enable navigation and route learning. Ventral subregion of the posterior cingulate = 23v; arcuate sulcus = as; calcarine sulcus = cas; corpus callosum = CC; cingulate sulcus = cis; central sulcus = cs; inferior occipital sulcus = ios; lateral sulcus = ls; occipitotemporal sulcus = ots; medial parietal area (also known as 7m) = PGm; principal sulcus = ps." (Figure adapted from Kravitz, D. J., Kadharbatcha, S. S., Baker, C. I., and Mishkin, M., A new neural framework for visuospatial processing, *Nature Reviews Neuroscience*, 12, 4, 2011, p. 120.)

to diagnose lesions of the visual pathways and ocular–motor system. They sometimes prescribe exercises for eye movement disorders, which are often performed with the assistance of an occupational therapist. Occasionally, an ophthalmologist will work with an orthoptist, an ophthalmologically trained therapist, to remediate eye teaming disorders, such as strabismus. However, ordinarily, ophthalmologists are mostly concerned with providing the medical or surgical support required in early rehabilitation or for later surgical intervention if spontaneous recovery and therapy fail to produce an acceptable result with a traumatic strabismus.

Neuro-ophthalmologists are ophthalmologists who have specialized in diagnosis and treatment of neurological dysfunction of the visual system. They are more likely to have some experience with rehabilitating the "visual software" or application of nonsurgical or pharmacological therapies for rehabilitation than are general ophthalmologists.

Optometrists specializing in vision therapy and/or rehabilitation are trained in diagnosis and nonsurgical treatment of more complex fixation, eye movement, or eye teaming (i.e., binocular) disorders as well as perceptual, cognitive, and integrative dysfunctions in the visual system. Usually, the treatment of such disorders is performed with the assistance of a vision therapy technician under the doctor's supervision. In an inpatient or rehabilitation center outpatient situation, occupational therapists working under a doctor's supervision or prescription will sometimes assist the patient with vision therapy for perceptual and sensorimotor dysfunctions or less complex eye movement and eye teaming dysfunctions. They may also assist with teaching new living skills to compensate for residual vision deficits.

Optometrists specializing in low vision assessment are trained in prescription of low vision aids for patients with reduced visual acuity and "field expanders," which may be required for patients with visual field defects. These doctors will often work with, or refer to, a low vision rehabilitation specialist, frequently called an *orientation and mobility specialist*, who can assist in teaching the patient new living and mobility skills to cope with his or her acquired visual deficit.

Because it is difficult to predict the effect of vision defects on driving, on-road assessment for patients with vision deficits that may impair driving are best performed by a certified driving rehabilitation specialist (CDRS). These specialists also provide training to assist in return to driving.

Vestibular system damage may cause nystagmus, vertigo and imbalance, and/or obstruct normal fixation and pursuit. In such a case, referral for vestibular workup to a professional equipped to perform eye movement recordings for diagnosis and to make rehabilitative recommendations may be helpful. Neuropsychological examination may help to give a broader perspective on visual perceptual dysfunctions. Finally, as with other types of rehabilitation following a TBI, visual rehabilitation may be significantly enhanced by the assistance of a counselor or psychotherapist to assist patients in understanding their new limitations and the need to rehabilitate as well as managing emotional sequelae, which can interfere with effective rehabilitation.

PREVALENCE AND IMPACT OF VISUAL DYSFUNCTION IN TBI PATIENTS

Because of the multifaceted nature of visual dysfunction and the broad distribution of visual functional areas in the brain, many, if not most, TBI patients suffer from some sort of visual dysfunction. When using visual symptoms to relate the dysfunction to the injury, clinicians must be aware that there are two common circumstances in which symptoms may onset weeks or months following the injury. The first is related to the fact that patients are, often, unaware of deficits following brain injury, and it is only as the functional demand increases that they become aware of their deficits. For instance, patients will report that they have no difficulty reading, but when queried whether they have read since their injury, they will state that they have not as they have been busy with rehabilitation of other things. Often they are unable to read and do not realize it because their rehabilitation and activities of daily living have been at much more basic levels. As the patient's level of functional competence increases, so do the functional demands, and new symptoms arise. The second common circumstance in which new visual symptoms arise in the months following the injury is when medications related to managing injury-related manifestations are changed as many medications commonly prescribed following brain injury have visual side effects.[12] These are also "injury-related" symptoms as the medications are necessitated by the injury.

Transient changes in refractive error, most often in a myopic direction, which may last for months or years, are common after TBI.[13–15] Accommodative (i.e., focusing) dysfunctions are also common[16,17] and may interfere with reading, fine depth discriminations, and rehabilitative therapies that are performed at near point. Near point tasks as well as balance, orientation, mobility, and daily living skills may be affected by visual field defects and binocular disorders as well as by dysfunctions in attention (e.g., visual–spatial neglect), visual perception, and spatial organization.[15,17–19] Binocular disorders can cause postural changes as the patient finds ways to either maintain fusion or enhance suppression of one eye by tilting or turning the head or torso.

It is often the case with TBI patients that eye-care professionals, untrained in diagnosing more subtle visual and ocular–motor dysfunctions, may dismiss patient complaints of headache, dizziness, inability to concentrate, blurred vision, fatigue, light sensitivity, or inability to read as due to emotional or other nonvisual etiologies. Although many of these symptoms may have nonvisual causes, a careful assessment of the visual system will often reveal the physiological or perceptual difficulty underlying the patient's complaint.[20] *Therefore, it is important that the TBI patient be examined by an eye/vision care provider who has a special interest in the area of neuro-, rehabilitative, or therapeutic vision care.* (See Appendix 26-A for a partial list of organizations that can provide educational materials or lists of member doctors who practice in this area.)

Gaetz and Weinberg have demonstrated deficits in visual event-related cortical potentials (VECP) in patients

with persistent symptoms from TBI classified as mild head injuries or concussions.[21] They conclude that patients with postconcussive symptoms frequently have persistent brain damage that cannot be visualized using CT or MRI techniques but can be elucidated using visual and auditory event-related potential techniques. Lachapelle et al. reached similar conclusions in another VECP study of patients with TBI.[22] Lachapelle's group later extended this research to the mild TBI (MTBI) population and demonstrated changes in VECPs to visual texture and visual cognitive paradigms; latency changes in the VECP following mild TBI correlated with vocational outcome.[23]

Magone et al.[24] found, in a retrospective case series of 31 patients with blast-induced MTBI, that, even years after the injury, 68% had visual complaints in spite of excellent distance visual acuity. Multiple MTBIs increased the probability of chronic visual symptoms. The most frequent complaints were photophobia and difficulty with reading. Convergence insufficiency and accommodative insufficiency were common in this population. Goodrich et al.[25] analyzed eye examination records for 50 blast-related (BR) and 50 non-blast-related (NBR) TBI patients. They found that more than 65% of both groups reported vision problems. Approximately 50% of the patients complained of reading difficulties. Photophobia was reported significantly more often in BR (65%) patients than in NBR (33%) patients. Saccadic dysfunction was measured more often in NBR patients (85%) than in BR patients (58%). They also found high rates of accommodative and convergence insufficiency in both groups. Pursuit dysfunction, fixation deficits, and visual field defects were common in these patients. Schlageter et al.[26] found that 59% of TBI patients admitted to an acute rehabilitation center had eye movement or eye teaming dysfunctions. More recently, the King Devick test of saccadic eye movements—a rapid number naming test—has been demonstrated to be a sensitive measure of sport-related concussion in multiple sports[27,28] and related to impairment on the Standardized Assessment of Concussion Immediate Memory test.[28] However, this sensitivity is limited to circumstances, such as sports teams, with which individual preinjury scores can be obtained; Silverberg et al.[29] found that the King Devick did not discriminate between those with and without MTBI in an emergency department setting. Cohen et al.[30] found convergence insufficiency (i.e., difficulty pulling the eyes inward as is necessary for binocular fixation on near targets) in approximately 40% of both TBI inpatients with recent injuries and follow-up patients 3 years postinjury. In the follow-up group, convergence insufficiency was positively correlated with duration of coma, dysphasia, cognitive disturbances, and failure to find placement in nonsupported work situations. Lepore[31] examined 60 patients with TBI and resultant strabismus. Among the 51 patients with nuclear or infranuclear findings, fourth cranial nerve palsies were the most common (39%), followed by third nerve palsies (33%), sixth nerve palsies (14%), combined palsies (10%), and restrictive ophthalmopathy (4%). Convergence insufficiency was the most common supranuclear dysfunction. Similarly, in 114 patients referred to an ocular motor clinic for visual disturbances following motor vehicle accidents, Fitzsimons and Fells[32] noted fourth nerve palsy in 36%, third nerve palsy in 25%, and multiple diagnoses in 25%. Aberrant regeneration was noted in 78% of third nerve palsies. Ciuffreda et al.[33] reviewed records of ambulatory patients, 160 with TBI and 60 with cerebrovascular accident (CVA) with associated vision symptoms. These researchers found accommodative and vergence deficits were most common in the group with TBI, and strabismus and cranial nerve palsies were most common in the group with CVA. Ocular–motor dysfunction was found in more than 85% of both groups. Goodrich et al.,[34] in a retrospective review of 100 veterans with TBI with (41%) and without posttraumatic stress disorder (PTSD), found one or more oculomotor or binocular deficits in 88% of the patients. Patients with PTSD were more symptomatic with photophobia, diplopia, and reading complaints, but did not demonstrate any differences in oculomotor or binocular deficits as a group from the patients without PTSD. PTSD was strongly associated with MTBI in this patient sample. The authors suggest that the organic brain injury caused the oculomotor/binocular deficits and that the hypersensitivity associated with PTSD may lead to increased symptom reporting.

Padula and Argyris[35] have identified a constellation of visual deficits, which they have termed *post-trauma vision syndrome* (PTVS). These deficits may include high exophoria or exotropia, convergence insufficiency, accommodative insufficiency, and ocular–motor dysfunction. Common symptoms include double vision or a perception of motion in stationary objects or printed material, blurred near vision, photophobia, eyestrain, and headache. Additionally, they have described visual–motor dysfunctions related to judgments of egocentric visual midline shifts associated with PTVS. These shifts create symptoms, including dizziness and balance problems, similar to those created by vestibular dysfunction.

Groswasser et al.[36] reported bilateral visual field defects in 14% of severe TBI patients. Ocular–motor defects in these patients were associated with poor recovery as defined by return to work or school. Bilateral visual field defects were more common in the poor recovery group, but this finding was not significant. A 15-year follow-up study of U.S. Vietnam veterans with penetrating head injuries showed that visual field loss and visual memory loss were negatively correlated with return to work.[37] In an assessment of successful versus unsuccessful TBI clients in a supported employment program, Wehman et al.[38] evaluated the functional limitations of those clients rated most difficult and least difficult to maintain in employment. The two areas of functional limitations that were significantly different between these groups were visual impairment and fine motor impairment. Najenson et al.[39] found that performance on the Raven Matrices Test—which is heavily loaded for visuospatial performance—was highly correlated with successful performance in the rehabilitated TBI patient's working life. McKenna et al.[19] examined the incidence

of visual perceptual impairment in patients with severe TBI and found, using the Occupational Therapy Adult Perceptual Screening Test, visual–spatial neglect in 45% of their sample. Visual–spatial neglect is frequently underdiagnosed in the brain injury population as the patient is unaware of the deficit, and it may or may not be concurrent with a motor neglect that cues the clinician into realizing that there is a problem.

Last, as reviewed by Murray et al.,[40] non-"neglect" types of attentional deficits in TBI patients have been considered in terms of information processing models rather than in terms of constructs, such as sustained attention or distractibility. Shum et al.[41] provide evidence for a four-step sequential information processing model with which attentional processes are considered as the sequential stages of 1) feature extraction, 2) identification, 3) response selection, and 4) motor adjustment. Children who had suffered severe TBI showed significant impairment on complex choice reaction time tasks designed to test each of these processing stages as compared to age- and gender-matched controls. Based on these findings, diagnosis and treatment of these primary processing disorders may be the most direct approach to treating attention disorders in TBI patients.

THERAPEUTIC INTERVENTION: WHAT AND WHY?

Plasticity and flexibility in the adult visual system

The amazing flexibility in modification of the vestibulo-ocular reflex as well as the visual perceptual apparatus has been demonstrated in normal adults by application of inverting prisms.[42] Initially when wearing these prisms, the world appears upside down and backward, but with continued prism wear, the vestibulo-ocular reflex reverses, and the visual perception reverts to normality. More recently, pre- and post-therapy fMRI[43] and voxel-based morphometry analysis of high-resolution MRI[44] studies with adults have demonstrated changes in cortex activity and cortical connectivity consistent with the rehabilitation techniques employed. Imaging studies of recovery following brain injury resulting in visual field defect demonstrate significant plasticity and rerouting of visual pathways to enhance function in both spontaneous recovery and following rehabilitation for visual field deficit (reviewed by Urbanski et al.[45]). Substantial neural plasticity is present in other areas of the adult visual system as demonstrated by orthoptic therapy remediation of amblyopia and strabismus in adults.[46–48] Freed and Hellerstein have demonstrated that the visually evoked potentials (VEPs) of adults with MTBI frequently normalize following application of vision rehabilitation techniques in contrast to VEPs of matched participants who do not receive vision rehabilitation.[49] Yadav et al.[50] demonstrated normalization of VEP amplitudes as well as visual attention in patients with MTBI following oculomotor vision rehabilitation. Schuett and Zihl[51] asked the question whether age matters in visual rehabilitation of visual field disorders following brain injuries. They found no age differences in successful response to compensatory oculomotor therapy for visual exploration and reading during visual field defect rehabilitation. Ocular-motor training has been demonstrated to be effective in many other vision deficits, such as accommodative dysfunction, versional eye tracking, and nonstrabismic binocular disorders in patients with MTBI.[52–54] In the non-TBI population, vision therapy and perceptual training has proven effective for treatment of many visual disorders, such as accommodative dysfunctions;[55,56] eye movement disorders;[57] nonstrabismic binocular dysfunctions, such as convergence insufficiency;[55,58,59] strabismus;[60,61] nystagmus;[62] amblyopia;[63] and some visual–perceptual disorders[64–67] in both adults and children. Most of these visual disorders may be suddenly acquired with a brain injury.

Remediation of ocular–motor and binocular disorders following TBI

Vision therapy has also been applied successfully to remediation of vision disorders secondary to brain injury.[68–73] Ron[74] studied six patients with ocular–motor dysfunctions resulting from TBI, such as saccadic dysmetria and decreased optokinetic nystagmus gain. Both saccades and optokinetic nystagmus normalized more rapidly with training as compared to control patients, and gains were maintained after cessation of treatment. Convergence insufficiency and strabismus have also been successfully remediated with vision therapy in brain trauma patients.[69,71,75] In an experiment to test the practicality of applying therapy to vision deficits in a short-term acute care rehabilitation setting, Schlageter et al.[26] failed to show statistically significant improvements from repeated baseline measures on pursuits and saccades in six TBI patients who received between 2 and 6 hours of therapy. However, when quality of eye movements was graphed against treatment, the slope increased (showing faster improvement) during therapy for both saccades and pursuits as compared to the baseline period. Although the occupational therapists and speech pathologists who administered the therapy were trained in a number of therapy techniques for saccades and pursuits, it became apparent during the study that "establishing a hierarchy of progressively more difficult exercises required a significant amount of training,"[26] (p. 447) and they may have found even better results had they used staff trained in orthoptic or vision therapy. Because of multiple demands on patient time in the acute care setting, treatment for visual disorders will generally not be completed in this setting. However, progress can be made, and visual dysfunction should be considered when making recommendations for the patient at discharge from acute care.

When surgical intervention is required for remediation of a residual posttraumatic strabismus, patterns of eye movement and teaming must be relearned. Fitzsimons and Fells[23] report that, among 92 TBI patients who had extraocular muscle surgery, 50% required more than one surgery,

and 30% more than two. Of these patients, 52% had satisfactory outcomes as defined by a satisfactory field of single binocular vision with tolerable diplopia (i.e., double vision) when shifting gaze to the sides. Another 27% had moderate outcomes defined as suppression or diplopia with the ability to comfortably ignore one image. Finally, 22% had persistent troublesome diplopia necessitating occlusion. Their success rates may have been even better had they used functional therapy in conjunction with surgery. Pre- and postsurgical application of therapy can be a useful adjunct to surgery in encouraging fusion, expanding the range of binocular gaze, and eliminating diplopia. *Unfortunately, it is common that the professionals who treat strabismus are dichotomized into those practitioners who apply surgery and those who apply functional therapies rather than having the two work as a team*. Those who apply surgery alone rely on the existing visual system to relearn binocular fusion without any guidance. Often, this does not occur. Those who apply therapy alone risk not offering their patients the full range of services to assist in the best possible outcome. As more eye/vision care professionals begin to treat TBI patients, we hope an integrated approach will become more widely accepted.

Management of other visual dysfunctions following TBI

In patients with visual loss as measured by decreased visual acuity or visual field, low vision devices, such as magnifiers (both optical and digital), special telescopes (some of which may be spectacle-mounted), or "field expanding" devices, can be applied. As our population has aged, more research and development has gone into rehabilitation for these types of visual loss, which are frequent sequelae of stroke and age-related eye disease. Therapy for homonymous hemianopia has been shown to increase speed and breadth of visual search and improve both objective and subjective measures of visual abilities on activities of daily living, including, in some cases, partial recovery of visual field loss.[76,77] Therapy for visual spatial neglect can be similarly effective.[78] Researchers at the Massachusetts Eye and Ear Infirmary have documented the effectiveness of using a multidisciplinary team, including ophthalmologists, optometrists, occupational therapists, and social workers, in increasing patients' functional ability during visual rehabilitation.[79]

Therapies for perceptual dysfunctions other than visual–spatial neglect have been previously applied in non-TBI populations by some educators, optometrists, psychologists, sports trainers, neuroscientists, and neuropsychologists.[66,80] Development of computerized therapies for perceptual deficits have made perceptual rehabilitation more accessible and applicable by other therapists, including occupational therapists.[81,82] As perception is dependent on reception, it is advisable to test for and remediate or manage any sensory visual deficits prior to testing for perceptual dysfunction other than neglect. Evidence[80,83] generally supports the efficacy of perceptual therapy following brain injury although one must be aware that substantial spontaneous recovery occurs during the first 6 months following the injury.

When to treat

The timing of therapeutic intervention has been a controversial issue. Patients who are diplopic should have vision examinations as soon as possible after they are medically stabilized. Appropriate application of prism, cling patches, or partial patching (discussed later) in the early weeks postinjury can give the patient some relief of symptoms as well as preventing maladaptations that must be trained away later. Application of either specialized patches or prisms during these early weeks requires frequent reevaluation and adjustment to keep pace with spontaneous resolution of visual defects.

Although there is evidence that some visual defects, such as muscle palsies and pareses, may spontaneously recover up to 12 months postinjury,[84] other evidence shows that, in general, untreated brain-injured persons do not spontaneously recover from binocular disorders, such as convergence insufficiency.[30] The decision about when to intervene is most appropriately determined by factors other than the hope of spontaneous recovery.

During the initial 3 months postinjury, a rapid resolution may occur in many visual defects as edema in the brain diminishes. After this time, although spontaneous resolution may still be ongoing, it is likely to be slower, and unwanted compensatory mechanisms, such as suppression, set in. Further, in patients who are struggling with such deficits as orientation problems or diplopia, failure to address these difficulties in a timely manner may lead to depression and a poor attitude toward rehabilitation when it is finally offered. Patients who are left to their own devices after the acute phase of medical rehabilitation is completed will find ways to survive with remaining deficits—often in ways that are not positive adaptations. Follow-up studies in untreated TBI patients show that they generally do not make continued functional progress, and they may even decline in function over the long run.[83]

Even with the most careful diagnosis, one cannot always tell which patients are going to respond to treatment. In the areas of ocular–motor and binocular dysfunction following TBI, reevaluation on a monthly basis can be used to determine whether the patient is making progress. If therapy has been consistent and intensive and no progress is being made, then compensatory measures should be prescribed. Gianutsos[85] suggests that, in cognitive rehabilitation, intensive rehabilitation with an initial goal of restoration of function should be applied for 6 months. If no progress is made, then a different approach should be tried. This seems to be a good rule for visual perceptual and visual memory rehabilitation with the modification that some compensatory strategies are often applied immediately to help the patient function while pursuing therapy.

A USEFUL MODEL FOR ORGANIZING VISUAL REHABILITATION

Moore[86] has emphasized the importance of considering functional units in the brain, taking into account contemporary metabolic maps that show brain function rather than thinking of the brain as it has been mapped in the last century into discrete compartments associated with individual functions. Although it is necessary to have an understanding of the neuroanatomy of the visual system in order to help formulate an appropriate diagnosis, knowing the neurons does not provide an adequate basis for guiding therapy. It is equally important to have a working model of visual performance to guide rehabilitation efforts and higher-order visual testing. Neuropsychological models of information processing or even of reading will often begin with a box labeled *visual input* or *sensory input*. Exposure to such models may give the nonvision specialist the impression that visual input and its involvement in information processing is discrete and simple enough to fit into such a box. Working without a model of visual processing may encourage attempts to rehabilitate splinter skills, such as convergence, in cases in which a more holistic approach is necessary to get the patient reading again or reoriented in space. Many therapy-oriented optometrists use a model of visual processing similar to that developed by Cohen and Rein[87] and shown in Figure 26.3. Figure 26.4 represents a simplified model that may help the practitioner keep the big picture in mind during testing and treatment.

Sensory input/reception

Visual system input, or reception, is dependent on formation of a focused optical image on the retina; healthy eyes; and healthy, intact pathways to primary visual cortex. Accommodation (the internal focusing of the eye mediated by the ciliary muscle) and vergence (the ability to make disjunctive or inward and outward movements of the eyes) are also an important part of getting visual input to the visual cortex without confusion. These two functions are tied together by neural feedback loops. As one expends accommodative effort (trying to focus closer), the accommodative effort drives convergence, pulling the eyes inward. As accommodation is relaxed, the eyes diverge, or relax outward, as for viewing distant targets. There is a similar, but lower, amplification loop from convergence to accommodation: As one exerts convergence effort, it drives accommodation. It should be obvious that a disruption in the balance between these two interacting systems—accommodative–convergence and convergence–accommodation—can cause serious dysfunction in eye teaming and focusing. There are useful models of such disturbances[88] reviewed by Ciuffreda.[89]

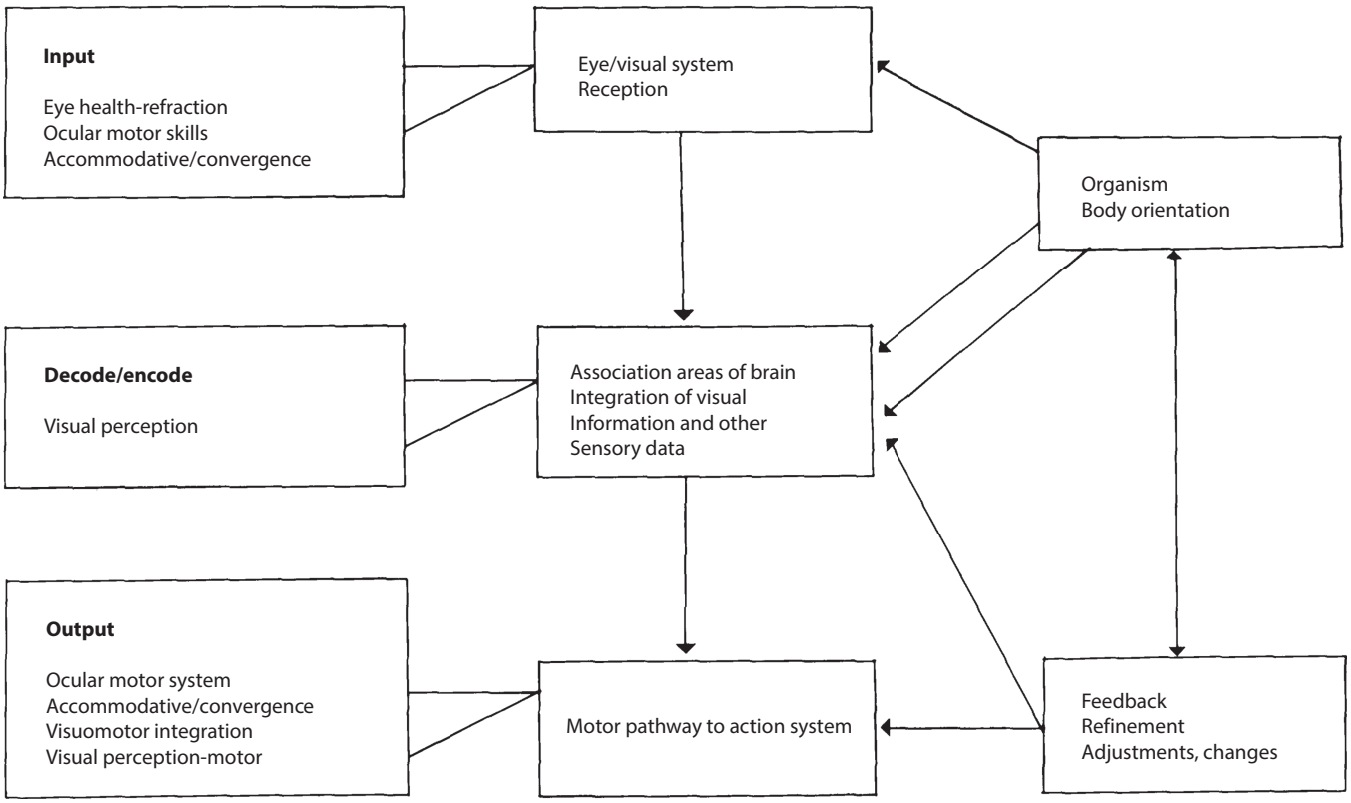

Figure 26.3 A model of visual function developed by Cohen and Rein, similar to that used by many optometrists to help guide vision therapy. (From Cohen, A. H., and Rein, L. D., *Journal of the American Optometric Association*, 63, 534, 1992. With permission.)

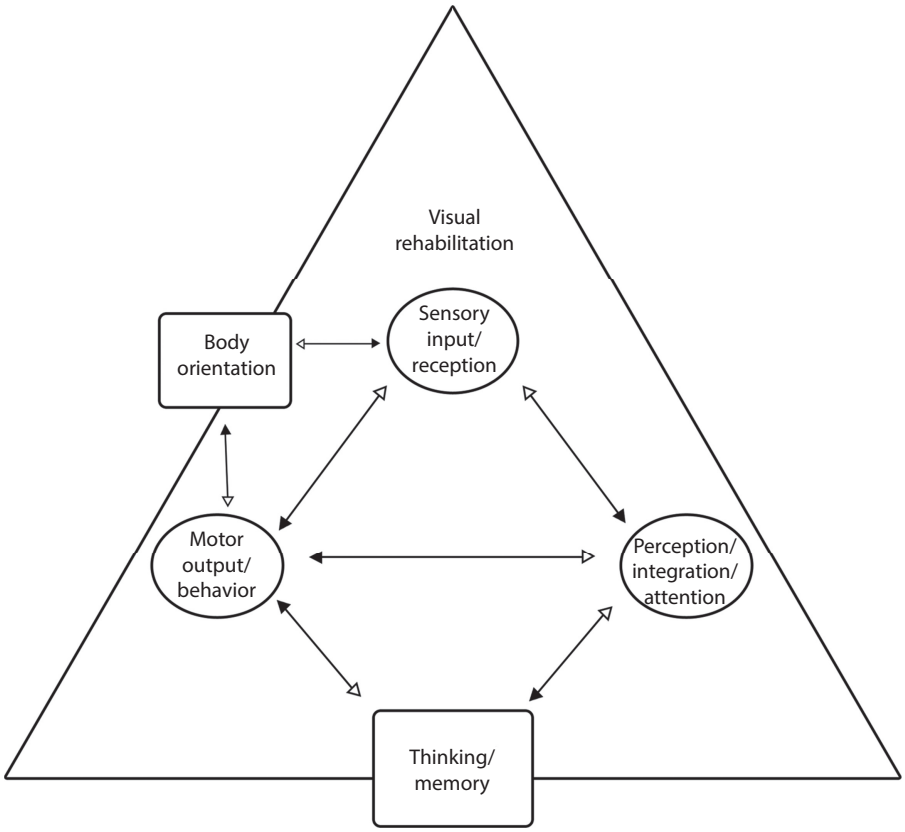

Figure 26.4 A modified model for guiding rehabilitation of the visual system. Functions within each processing area (circles) are as delineated in the original model by Cohen and Rein.[59] Closed head arrows indicate the major direction of information flow. Note that all arrows are bidirectional; information flow is bidirectional in most known pathways in the visual system,[2] and other bidirectional influences are explained in the text.

Visual reception is also dependent on the ocular–motor skills—that is, full range of motion of the extraocular muscles, the ability to fixate the target of regard, track it if desired, or saccade to another target efficiently and accurately. These abilities are dependent on feedback from areas that monitor head and body orientation and movement as well as those areas that monitor feedback from the ocular–motor drivers. The map of saccadic pathways in the brain (Figure 26.5) demonstrates the complexity of even the seemingly simplest of these ocular–motor skills. Reception ends at the primary visual cortex at which the initial binocular combination of input from the two eyes occurs to allow for fusion and stereopsis. The input is processed as color, contour, contrast, and depth.

Perception/integration/attention

Visual perception and integration are dependent on intact neural communication within visual processing areas and pathways between these processing areas as well as intact reception. Current trends in cognitive neuroscience implicate recurrent processing in the primary visual cortex (i.e., feedback from higher cortical processing areas to primary processing areas) as critical in awareness of visual input or visual perception.[90,91] Not only does damage to lower visual processing areas decrease activity in higher processing areas through loss of feed-forward (e.g., occipital to parietal and parietal to frontal areas) connections, but damage to higher processing areas decreases activity in lower level processing areas through loss of feedback connections.[10]

Integration of visual information is also dependent on pathways to and from processing areas mediating other sensory and motor functions. Much of the cerebral cortex is involved in visual processing with close to 300 intracortical pathways between the visual areas. Therefore, it is important to maintain a holistic model of the functions of this stage of processing so that one can test for and address functional loss with some guidance from available topographic details of the injury.

The major functions of this stage in the model are organization of space and motion, form perception, and object recognition[87,92] as well as integration of vision with the other senses and motor system input. Visual attention or awareness is also included here. Interfaces with thinking and memory processes are not in the original model (Figure 26.3) but should be added at this stage in a bidirectional manner as in the modified model in Figure 26.4. Our percepts feed into our memories and influence how we think, and our thinking and memories influence our perceptions and behaviors.

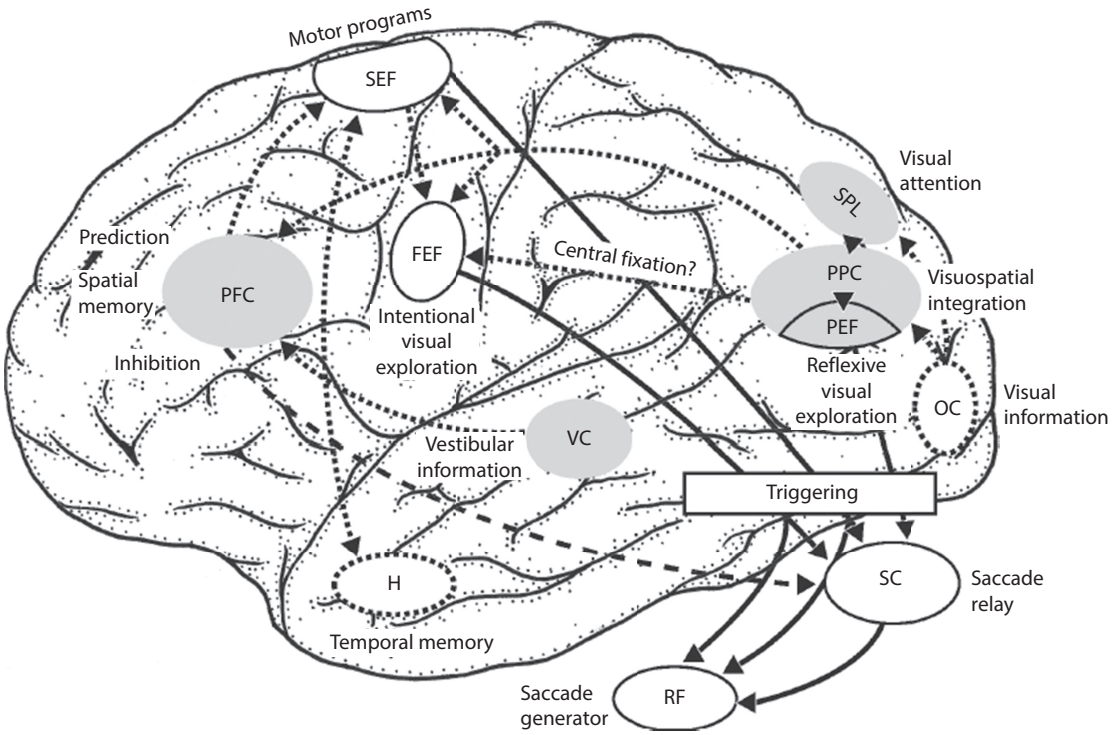

Figure 26.5 "…pathways for saccadic eye movements. Note that some of the arrows are bidirectional. FEF = frontal eye field; H = hippocampus; OC = occipital cortex; PEF = parietal eye field; PFC = prefrontal cortex; PPC = posterior parietal cortex; RF = reticular formation; SC = superior colliculus; SEF = supplemental eye field; SPL = superior parietal lobule; VC = vestibular complex." (From Helvie, R., Neural substrates of vision, In *Vision Rehabilitation: Multidisciplinary Care of the Patient Following Brain Injury*, Eds. Suter, P. S., and Harvey, L. H., CRC Press, Boca Raton, FL, 2011, p. 62. With permission.)

As discussed in the physical substrates section of this chapter, two major concurrent vision processing streams proceed forward from the occipital cortex: the dorsal stream to the parietal lobe, which then trifurcates into further processing streams, and the ventral stream, which is a recurrent occipital–temporal lobe pathway (Figure 26.1). The dorsal stream mainly carries information originating from magnocellular ganglion cells; this stream is first identified, anatomically, at the lateral geniculate nucleus where large magnocellular ganglion cells are segregated from the smaller parvocellular ganglion cells. The ventral stream mainly carries information originating from parvo cells.

Magno cells are, in general, sensitive to large contours, lower contrast, and faster temporal frequencies and are retinotopically distributed more peripherally than parvo cells (reviewed by Bassi and Lemkuhle[93]). Some magno cells are color-sensitive, but at least half are insensitive to color.[94] Approximately 20% of magno cells originating in the retinas are sent to subcortical systems for maintenance of diurnal rhythms, pupillary control, and survival-level orienting and balance. The rest of the magno system is preserved, in a relatively segregated manner, through the primary visual cortex and then as the dorsal stream to the MT area for motion processing (including optic flow, which keeps us oriented when moving through space) and from there to posterior parietal cortex for cortical processing of object localization and visual attention. When damaged, the posterior parietal cortex and the pathways to the frontal cortex arising from the parietal cortex are major substrates for visual–spatial neglect. From the parietal cortex, the dorsal stream trifurcates into a parieto–prefrontal pathway for spatial working memory, a parieto–premotor path for visually guided action, and a parieto–medial temporal pathway for spatial navigation.

Parvo cells, in general, transmit more slowly than magno cells and are more sensitive to color, high contrast, and detailed stimuli; they are the origin of the information carried in the ventral stream. The ventral stream, ultimately, traverses to the inferior temporal cortex and is involved in object perception (discussed later). The cortical dorsal and ventral streams maintain both separate and interactive functions. "Where" the object is and "what" the object is must be integrated in order to make sense of the world. However, research shows that it is possible to selectively interfere with memory for either "what" or "where."[95] Also, it can be demonstrated, electrophysiologically, that spatial attention has a different effect on each of these two pathways.[96]

In previous work elucidating the dorsal and ventral processing streams, Milner and Goodale[97] presented evidence that the dorsal stream provides for visually guided action and programming of the movements involved in those actions, and the ventral stream provides for object perception and planning (separate from programming movement). Destruction of the dorsal stream creates optic ataxia or the

inability to program reaching for objects, and destruction of the ventral stream creates loss of object perception and planning, such that one might reach accurately but grasp the wrong portion of an object to use it as the patient does not know visually what the object is.

In addition to the cortical dorsal stream, an extrageniculate, "ambient" midbrain visual system[98,99] processes information both directly from the retina and from the striate cortex to organize orientation in ambient space, again, mainly from magnocellular input. Organization of space and motion by both the cortical dorsal stream and the midbrain ambient system requires interpretation of reception from visual sensory substrates, ocular–motor drivers, and from substrates reporting body orientation and motion in order to ascertain the spatial location of objects in relation to ourselves. This analysis allows us to determine whether we are moving, the external stimulus is moving, or some combination of both. The midbrain system is faster than the cortical magno system and mediates much of our survival-level orienting, head movement, and saccadic eye movement. It is also involved in perceptual coherence. The information from the different senses arrives at the brain with different latencies, both due to external differences (think of the lag between lightning and thunder, but at much shorter distances) and internal differences in neural transmission times from receptor organs.[100] The information from various senses associated with a single event must be matched together, largely coordinated in the superior colliculus.

Form perception and object recognition in the ventral pathway require figure–ground segregation, form constancy, visual closure, and some processing of spatial relationships. These functions interact with visual reception in that the ability to perform these functions may be limited by visual field loss or degraded visual acuity, contrast sensitivity, or fixation.

Feedback from both accommodation and convergence helps localize objects in depth.[101] A good example of how perception/integration in the dorsal pathway are affected by reception is presented by the problem of motion perception in strabismus (i.e., eye turn). Strabismus is a reception error with which the two visual axes are not aligned on the object of regard. In strabismus, not only is depth perception limited by loss of stereopsis (i.e., 3-D vision), which requires alignment of the eyes to discern fine retinal disparities, but also the perception of space during motion is distorted. Optic flow—the pattern of movement of background around a fixated target—is disrupted when the two eyes are not simultaneously fixated on the target. For instance, when one fixates a signpost that one is moving past, the optic flow of the foreground on the retina is perceived as moving in the opposite direction of your movement, and the optic flow of the background behind the signpost is perceived as moving in the same direction as you are moving. In a crossed strabismus, the alteration of direction of optic flow changes in front of the object of regard, where the visual axes meet, such that the signpost would be sitting not in the center of the change in direction at a stable point, but in the midst of the background directional optic flow, moving with you.[102] The opposite would be true for an outward eye turn with which the visual axes meet behind the target of regard.

Cross-modality integration is dependent on intact pathways to and from the neural substrates mediating the other senses as well as subcortical and cortical processing to make matches between them. Object perception includes integration with the visual input of information about the object from our other sensory modalities, e.g., the lemon smells "lemony," is smooth and a bit oily to the touch, tastes sour, etc.

Visual awareness, although most often taken for granted by rehabilitation professionals, is surprisingly often disrupted in TBI and other pathology of the visual system. Patients with neural damage to the visual system are, often, unaware that there has been any change in their function. It is only when one demonstrates to them, on a visual field printout, a line bisection or cross-out test for visual neglect or a processing speed test that their performance is grossly subnormal that they begin to understand that there is a visual deficit.

Considering the covert nature of many visual deficits following brain injury, it becomes clear how such a pervasive system as the visual system can be so frequently ignored in the rehabilitation setting as neither patients nor practitioners may be aware that the patient's symptoms are visual in origin. Those systems that traditionally receive the most rehabilitation effort tend to be those that are overt in nature (e.g., language reception and expression, vestibular dysfunction, and motor dysfunction) even though the representation in the brain (and, therefore, the impact of TBI) is often considerably less for these systems than for the visual system.

Motor output/behavior

Organization of body movements in relation to visual targets is mediated, most directly, by the posterior parietal areas and angular gyrus. Three major pathways connect these areas with the motor areas: one via intracortical connections, one via the basal ganglia, and one via the cerebellum.[103] Individual functions of these three pathways are not well understood.

The percepts of our visual world that we construct during reception and perception are used to guide further motor activity, both within the visual system and in visually guided motor activity, such as mobility or eye–hand coordination. These percepts direct our ocular–motor activity and eye pointing. They influence the frontal lobe areas, which generate executive commands for voluntary eye movements so that we may regard objects at will rather than in a purely stimulus-driven manner. They are involved in direction of the next movement whether for perception or for action. In short, these visual percepts and the resultant thought processes dependent on them are the foundations for much of the everyday behavior of a sighted person.

Visual thinking/memory (visual cognition)

Much of our thinking and memory is processed as part of the visual processing stream. Visualization of complex problems or forms is one method of problem solving and organizing that does not require language. Although visual thinking, in general, is typically addressed by education in the rehabilitation setting, the skill of visualization—the ability to generate and manipulate endogenous images—is typically addressed by visual rehabilitation providers. Memory is a concept with which every person is familiar, and, yet, it is poorly understood. Memory has both short- and long-term components. In neuropsychology, long-term memory is often subdivided into procedural, perceptual representation, semantic memory, and episodic memory.[104] Short-term or working visual memory is encoded and stored separately from auditory and haptic memories[105] and can be broken down into spatial memory (thought to be processed by the magno stream) and object memory (thought to be processed by the parvo stream).[96] Rehabilitation of visual memory most often involves rehabilitation of visual aspects of working memory as well as the ability to transfer this information to long-term perceptual representations.

ASSESSMENT AND REHABILITATION OF THE VISUAL SYSTEM

Assessment and rehabilitation of sensory input/reception

In the rehabilitation setting, testing and treatment of visual dysfunction has traditionally centered on the higher-order perceptual disorders, tending to ignore reception.[106] It is important to keep in mind that many of the higher-order visual abilities are dependent on sensory input and ocular–motor functions involved in reception.

EYE MOVEMENTS

Eye movements can be classified into those that shift the direction of gaze (i.e., saccades, smooth pursuits, and vergences) and those that hold the direction of gaze steady (i.e., the vestibular-driven, optokinetic, cervical–ocular, and fixation mechanisms).[107,108] Vergences are discussed later under binocular disorders. Optokinetic nystagmus (OKN) may be used in testing and therapy for other visual dysfunctions, but deficits in OKN are not generally considered and rehabilitated in the TBI population as visual deficits. This may be because detection of deficits in OKN requires more sophisticated eye-movement monitoring than is available in most vision practices.

Saccades

Saccades are the fast eye movements one makes to change the object of fixation; the eyes seem to jump from one target to another. They are the movements that take us from word to word in reading and from object to object in driving. Saccades during reading may be affected in a bottom-up manner, that is, the eye movement controllers have been damaged, or in a top-down manner, that is, the ability to comprehend text has been damaged, causing more regressions and less accurate fixations due to poor guesses about what is coming next.[109] Patients with acquired primary saccadic dysmetria (i.e., saccades that overshoot or undershoot the target) will often complain of slow and inaccurate reading.

Voluntary saccades, which allow us to change our gaze at will, and stimulus-generated or reflexive saccades, with which we correct our gaze or saccade to a target that has attracted our gaze, are controlled, in part, by separate brain centers and should be addressed separately. It is also important to assess the ability to inhibit saccades to peripheral targets. This may be a function of the fixation mechanism discussed later. Simple observation while the patient makes voluntary saccades between two targets or reflexive saccades to alternately lit targets gives a qualitative measure of latency, speed, and accuracy of the saccades. This procedure should be done at least for lateral saccades in right and left gaze orientation. Each eye should be observed independently. The targets should be relatively close together as most natural saccades are less than 15°,[108] and large excursions encourage hypometric saccades or recruit head movement. Scoring systems for these observations are reviewed by Griffin.[110]

A more quantitative approach, which can provide additional data, is provided by the Developmental Eye Movement Test (DEM).* This is a timed test in which the patient must saccade to numbers that are arrayed on a page and name them as quickly as possible. The DEM is a substantial improvement over earlier saccadic tests of this genre in that timed baseline measurements are taken with the patient reading columns of evenly spaced vertical numbers so that difficulties with decoding or verbal expression can be differentiated from difficulty with the ocular–motor task. Next, a series of horizontal rows of digits are read. The number of errors and the time required to read all of the digits are combined into separate scores for the vertical and horizontal tasks with a higher score being slower or less accurate performance. A high ratio of horizontal score to vertical score indicates a saccadic problem. The DEM does not differentiate between difficulties in speed, latency, or accuracy although error scores give some indication of the latter. Normative data by age is provided for times and error scores on both the vertical and horizontal tasks as well as the ratio between them. Note, however, that this test concentrates on reading-type saccades, mostly left to rightward, and should be used in conjunction with other tests. As mentioned earlier in this chapter, a simpler test, the King Devick test of saccadic eye movements, has been demonstrated as a useful sideline indicator of sports-related concussion when preseason baselines for each player can be obtained to compare to postinjury scores.

* Developmental Eye Movement Test: Available from Bernell Corporation, Mishawaka, IN, www.bernell.com

A variety of instruments have been designed to objectively monitor and record eye movements. These eye-movement monitors give the most easily interpreted data but are less frequently used in the clinical setting due to issues of availability and expense.

Ordinarily, when training, saccades, latency, speed, and accuracy are lumped into the same scores; one trains for accuracy and then for speed, which improves as any one of the three parameters improves. Therapy may start with something as simple as saccading from one penlight to another as they are alternately lit in a dim room and progress to complex search tasks, such as finding the next in a series of letters or numbers scrambled on a page. Instruments, such as the Wayne Saccadic Fixator* or the Dynavision,† with various programs for training saccades in combination with eye–hand coordination, are both useful and motivational. A number of computer-based programs have also been developed for orthoptic treatment of ocular–motor and binocular disorders. If difficulty inhibiting saccades or sustaining fixation is noted, one can apply therapies, such as making saccades only on a designated command to each in a series of targets. The ultimate goal of therapy is to develop fast, accurate saccades, both large and small, which can be sustained and performed with a high degree of automaticity. The latter is tested by adding a cognitive load, such as addition or spelling, as the patient does a saccadic task. This is an important concept in much of the visual therapy of eye movements. When a cognitive load is added, performance of the ocular–motor task will break down in patients *who are allocating excessive resources to what should be, for the most part, an automatic task*. Griffin[110] and Press[111] have written excellent texts for vision care providers interested in learning about vision therapy programming and specific therapeutic techniques. Many of these therapy techniques may be prescribed by vision care practitioners for application by occupational therapists in the rehabilitation setting.

Pursuits

Pursuits are the smooth eye movements used to follow a moving object and hold a clear image of it stationary on the retina. They are complementary to the vestibulo–ocular reflex in holding images stationary on the retina when we are moving. Pursuits are limited in speed to about 30° per second. Attempts to track a faster target cause saccadic intrusions and "cogwheeling" of the movement. Pursuits are usually tested at the same time that the range of extraocular muscle motion in each eye is tested. Simple observation gives qualitative information about the ability to track a target to the full range of motion of each of the extraocular muscles monocularly and then binocularly. The ability to track should be judged on smoothness, accuracy, stamina, and the ability to track without head movement. As with saccades, a cognitive load should be applied to judge automaticity. Griffin[110] outlines systems for scoring pursuits.

Therapy for pursuits is often combined with extraocular stretching exercises relieving restrictions or contractures of the extraocular muscles by following targets to the farthest peripheral directions of gaze possible. These exercises are also important in the initial stages of therapy for binocular disorders. If there is any deficit on monocular testing, extraocular movements are trained monocularly prior to training binocularly so that equal facility is gained with each eye before adding a fusional load to the task.

For most vision therapy, one goal is to make the patient self-monitoring. Pursuit therapy is most effective when patients can be made aware of jerkiness or saccadic intrusions in their pursuits so that they can try to correct them. Many patients will be able to feel their eyes jump when their attention is directed to noticing interruptions in their smooth pursuit. However, in many TBI patients, proprioception from the extraocular muscles seems to be diminished or absent so that they are unable to feel when their eyes jump. In such cases, cues can be added to assist the patient. One technique is to use afterimages to tag the fovea by using a camera flash that has been masked off except for a small central target on which the patient fixates while the flash is triggered. The patient tries to maintain this afterimage on the pursuit target without interruption. A simpler technique that is sometimes effective is to have the therapist tell patients every time their eyes jump until the patients can begin to feel it for themselves.

Various instruments, from rotating discs with targets on them to computer-generated pursuit games, have been designed for facilitating pursuit therapy under both monocular and fused conditions. The ultimate goal of therapy is to be able to sustain smooth pursuits with either or both eyes in all fields of gaze with a high degree of automaticity, initially without moving one's head and then adding head and, later, body movement.

Vestibular-driven eye movements

Vestibular-driven eye movements—in particular, the vestibular–ocular reflex (VOR)—help hold the visual world steady as we move within it. Patients who do not spontaneously adapt to damage affecting the VOR may complain of oscillopsia or rhythmic movement of stationary objects. One way to test for a VOR problem is to have patients read a near point acuity card while shaking their head side to side and then up and down. In the case of a VOR dysfunction, the visual acuity will be severely degraded as compared to an acuity taken with the stationary target.[112] Although therapy techniques have not been specifically developed for VOR dysfunction, applying the afterimage techniques discussed previously with the patient attempting to stabilize the afterimage, initially while sitting still and, later, with head movements, may give enough extra feedback to assist in recovery. Whether the patient recovers or learns to adjust to the movement, oscillopsia should be taken into consideration in driving rehabilitation.

* Wayne Saccadic Fixator: Available from Wayne Engineering, Skokie, IL. www.wayneengineering.com

† Dynavision: Available from Dynavision International, Markham, Ontario, Canada. www.dynavisioninternational.com

The VOR must be coordinated with the cervical–ocular reflex (COR), a proprioceptive mechanism, which also contributes to gaze stabilization. In the COR, eye movement is elicited by rotation of the neck. The VOR decreases with age, and the COR covaries, in the opposite direction, increasing with age.[113] The COR is increased in whiplash, interfering with the synergy between COR and VOR, and may contribute to symptoms in these patients, including dizziness and vertigo.[114] In the differential diagnosis of dizziness and balance disorders, the COR must be considered along with the visual and vestibular contributions.

Fixation

Fixation, or the act of holding gaze steady on a target, was once thought to be a function of the pursuit system at zero velocity. This may be why fixation, itself, is seldom evaluated except in relation to strabismic amblyopia. However, recent evidence implicates an independent visual fixation system, perhaps located in the parietal lobe.[107] Disturbances in fixation may be considered in terms of inability to sustain fixation as well as inability to fixate centrically and steadily. The former can be easily observed by having the patient hold fixation on a target for a minute. The ability to fixate steadily and centrically is only observable with special techniques. The easiest, most objective measure is with a visuoscope or, similarly, an ophthalmoscope with a central target. The examiner looks into the patient's eye with the scope, which projects a target onto the retina. The anatomy of the posterior pole of the eye and the projected target are viewed simultaneously. The patient is instructed to fixate the target while covering the other eye. The stability of the foveal reflex and centricity with regard to the target are easily observed in this manner. Other methods require reliable subjective feedback. For instance, the Haidinger brush, an entoptic phenomenon that marks the fovea, may be elicited with an instrument such as the Macular Integrity Tester* with which the patient fixates a target and reports the location and stability of the Haidinger brush in relation to the fixated target.

In the case of inadequate ability to sustain fixation, the first step is to rule out refractive, binocular, accommodative, or other ocular–motor dysfunctions that may lead to asthenopia (i.e., eyestrain and/or headache) or discomfort. Such dysfunctions may make extended viewing aversive. They are also remediable, and a primary attention or fixation mechanism dysfunction might not be.

Unsteady or eccentric fixation is most typically encountered as a developmental phenomenon associated with strabismic amblyopia. In this manifestation, it causes decreased visual acuity but is seldom accompanied by asthenopic symptoms. There is an effective arsenal of therapeutic techniques to routinely remediate developmental eccentric fixation.[36,110]

* Macula Integrity Tester: Available from Bernell Corporation, Mishawaka, IN, www.bernell.com

Unfortunately, unsteady fixation that is acquired following TBI may cause asthenopic symptoms as it may be bilateral rather than unilateral, and it may be more resistant to treatment.

BINOCULAR DYSFUNCTION

Accommodation

Accommodative dysfunctions are common in the TBI population.[15] They can cause blur or asthenopic symptoms at near point as well as slow focus change from distance to near and back. A *simple near point acuity test does not rule out an accommodative problem* because it only indicates whether the patient can momentarily hold focus at near point. It does not indicate either that patients can sustain that focus or that they have any focusing flexibility. Objective techniques, such as near point retinoscopy performed while the patient processes visual information (e.g., reading or active involvement in viewing a picture), give an accurate assessment of the patient's lag of accommodation and ability to sustain accommodation on a near point task. Use of such tools as convex to concave lens flippers (i.e., devices with two pairs of lenses for viewing—one pair of convex lenses, which requires that accommodation relax to clear the target, and one pair of concave lenses, which requires accommodative effort to clear the target—set into a holder so that one can flip between the pairs of lenses) of various powers can give measurements of facility. These can be used as a subjective test with patients reading small print as they are able to clear it or as an objective test during retinoscopy. As discussed previously, accommodative difficulties can cause convergence dysfunction, and convergence difficulties can cause accommodative dysfunction. In many cases, it is impossible to tell which problem is primary.

Typical treatments for accommodative dysfunctions are vision therapy or convex lenses worn either as single vision reading glasses or bifocals. In a prepresbyopic patient, vision therapy is an effective way to improve the amplitude and facility of accommodation, provided that the innervation subserving the function is sufficiently intact. Near-to-far focusing jumps and concave-to-convex lens jumps with near point targets may increase both amplitude and facility. Associated vergence difficulties must be treated in conjunction with the accommodative problem for effective remediation. If rehabilitation of accommodative function is not possible in the young patient, compensatory convex reading lenses should be prescribed, generally in a bifocal format. Some practitioners have suggested that bifocals should not be used for patients with brain injury or that only lined bifocals should be used. However, a bifocal with the reading portion set low so that it is not a safety hazard during mobility, is generally much easier to use than having the patient keep track of two pairs of glasses and figure out when to use which. In cases in which lenses but no active vision rehabilitation therapy or only home vision rehabilitation therapy are being applied, the bifocal should be prescribed as a standard lined bifocal. In cases in which the bifocal add

is less than +2.00 D and the patient is undergoing in-office vision rehabilitation therapy, many patients do well with a "no-line" progressive bifocal as the therapy helps them adapt to the distortions in the progressive bifocal, and they receive the added advantage of clarity at intermediate distances, such as grocery store shelves, faces in conversation, and computer monitors. There are, of course, cases in which the patient has limited down gaze or in which the bifocal creates too much visual confusion to be applied. In these cases, separate reading glasses are indicated. Often, when separate reading glasses are required, the patient requires a great deal of cuing and support in order to get the proper glasses on their nose for various tasks.

Nonstrabismic binocular disorders

Nonstrabismic binocular disorders are those eye-teaming difficulties that do not result in a frank strabismus (eye turn). Convergence insufficiency—difficulty pulling the eyes inward for near work—may be the most common nonstrabismic binocular finding in TBI patients. *Convergence insufficiency will often be missed by the simple pushup or near point of convergence test*. Krohel et al.[75] found that six of 23 TBI patients with convergence insufficiency had a normal near point of convergence, but showed abnormal convergence reserves on prism testing. Prism vergence ranges should be mandatory in the visual evaluation of the TBI patient. Convergence insufficiency can lead to fatigue, headache, tearing, blurred vision, and eyestrain.[50] Often, it will cause skipping of words when reading or transpositions when reading digits in numbers as the eyes struggle to converge after each saccade.[57] High exophoria (i.e., nonstrabismic outward resting posture of the eyes) is also a common finding in TBI patients. Padula[11] hypothesizes that exo-deviations of the eyes following TBI are caused by damage to the midbrain structures that integrate ambient vision and spatial orientation.[99] This would be anatomically consistent with simultaneous damage to the mesencephalic structures involved in convergence control.[30] Padula et al. have described PTVS,[35,115,116] a cluster of common posttraumatic visual deficits that may include high exophoria, convergence insufficiency, and accommodative dysfunction. Using brain response testing (VEPs), Padula et al.[116] demonstrated that the amplitude of the visual event-related cortical potential (VEP) is decreased in PTVS and that application of binasal patches or low amounts of bases in prism cause a significant increase in the VEP amplitude. In partial replications of the Padula et al.[116] findings, Ciuffreda et al.[117] and Yadev[118] found increased VEP amplitude with binasal patching in participants with MTBI, in contrast to the neurotypical participants whose VEP amplitudes decreased in the binasal patching condition. Ciuffreda et al.[117] also found that symptoms were reduced and visuomotor tasks were improved in MTBI patients wearing binasal patches.

The work of Padula et al.[116] also provides a clinical protocol for diagnosing PTVS using the VEP. If PTVS is diagnosed or suspected, early application of base-in prism and/or binasal patches may be profitable in treatment.

Prior to treating other binocular disorders, monocular eye movement and accommodative dysfunctions should be treated insofar as possible. Treatment of exo-binocular disorders may include prism in reading or distance lenses, binasal patches, or therapy. One difficulty with putting base-in prism in lenses is that patients may prism-adapt over a matter of days or weeks, developing the same phoria through the prisms as they had prior to introduction of the prisms. In such cases, the prescription of base-in prism increases the tonic error in binocular posture, leading some optometrists to argue that prism is poison. However, in a significant number of patients, base-in prisms provide an immediate reduction of symptoms, and the patients do not prism adapt. The difficulty is in determining for which patients this will be the case. In-office, short-term trials may help in this decision. In any case, patients wearing base-in prism in their habitual spectacles should be followed carefully. If they prism adapt, additional prism should not be prescribed.

Besides use of base-in prism, Padula and Shapiro[16] recommend use of bitemporal or binasal occluders (i.e., occluders covering only the temporal portion of both lenses or nasal portion of both lenses, respectively) applied to the patient's habitual spectacles for nonstrabismic visual dysfunctions. They suggest that bitemporal patches may reduce confusion by reducing input from the midbrain ambient vision system when the patient is attempting focal tasks, such as reading. Binasal patches may be used in an effort to increase patients' awareness of their ambient vision while eliminating physiological diplopia (i.e., the normal diplopia for objects in front of or behind the plane of fixation), which may initially cause confusion in the post-TBI patient. They also argue that this encourages reorganization of the midbrain-based ambient visual system, which is critical for visuospatial organization and vision during movement.

Vision therapy for poorly compensated exophoria or convergence insufficiency should include fusional exercises to improve the amplitude of and the ability to sustain convergence as well as the speed of reflex fusion. Convex lenses may be used to work fusional convergence through the accommodative–convergence loop. Viewing through the convex lens relaxes accommodative–convergence so that the patient must exert more fusional convergence to avoid diplopia. Prisms can be used for manipulating images, causing the fusional vergence system to respond to the displaced image. Polarized or anaglyphic materials may be used in order to create second- or third-degree fusion targets (i.e., flat fusion or stereoscopic fusion, respectively), which can be manipulated to expand vergence ranges. At the same time, matches are developed between the ocular–motor feedback and position-in-space interpretation. Many specialized instruments have been developed for treatment of such binocular disorders. Some of these techniques may be prescribed for application by occupational therapists. Many of these techniques require more experience in vision therapy or more extensive instrumentation for effective application and, therefore, need to be performed in the vision care setting.

Esophoric (i.e., nonstrabismic inward resting posture of the eyes) deviations of binocular vision are less common. This may be due to anatomical considerations or because esophorias are more difficult to compensate for and are more likely to break down into a strabismus. Poorly compensated esophoria will often cause eyestrain or headache around the eyes or temples. Treatment may include use of convex lenses for near work, base-out prism, and vision therapy similar to that described for exo-deviations. The same cautions regarding use of prisms apply here—perhaps even more so as base-out prism is more difficult to remove once the patient has become dependent on it.

Strabismus

In strabismic deviations secondary to TBI, diplopia causes disorientation as well as difficulty with spatial judgments, eye–hand coordination, mobility, and reading. Patients will often squint, close one eye, or assume head turns or tilts in order to try to block one eye or to keep objects in a field of gaze where they are able to fuse. In children, suppression and amblyopia may result. Patients who are diplopic should have a visual examination early in their rehabilitative program. Assessment of refractive status, binocularity, and ocular health do not require verbal communication from the patient. The same objective techniques that one would use to determine these conditions in a 4-month-old infant can be applied in the TBI population when necessary. Prisms or partial patching (as discussed later) can be prescribed to eliminate diplopia so that other ongoing therapies can be more effective. Any time that prisms or patches are prescribed, frequent follow-up is required to keep pace with spontaneous and therapy-related recovery.

Fresnel (flat, stick-on) prisms may be applied in an effort to reestablish fusion at the angle of the deviation. Lenses may also be applied in a therapeutic manner, using the accommodative–convergence relationship to mediate the angle of the deviation. For patients who are able, therapy is then applied as described previously for nonstrabismic errors, creating equal, efficient monocular skills, followed by vergence exercises combined with fusion, depth, and spatial localization training. Initial attempts at reestablishing fusion in adjustable instruments or with variable prisms may be met with horror fusionis–like responses with which the images from the two eyes will approach each other and then jump to the other side or may be superimposed but not fuse into one object with the percept of depth.[119] The prognosis for recovery is best for patients with horizontal strabismus, uncomplicated by vertical deviations. However, vertical deviations will often resolve with therapy or as therapy is applied to the horizontal component of the strabismus. Residual vertical deviations can often be managed with prism ground into the patient's lenses. Patients who are not able to perform vision therapy for remediation of their strabismus are generally managed over the long term with patches and prism. They may also be managed surgically beyond the time period when spontaneous recovery might continue to lessen the angle of deviation.

Traditionally, TBI patients have been advised to use constant patching of one eye to resolve diplopia. However, this has undesirable consequences, such as loss of peripheral vision on the patched side while patched and disuse of the patched eye, which may lead to suppression and/or diminish the chances of spontaneous recovery of fusion. *Partial* patching to eliminate diplopia or *patching for limited time periods* to facilitate other therapies is more desirable. If patients are unable to access rehabilitative vision care in a timely manner and diplopia is a major problem, patching the eyes on a daily alternating schedule may minimize the detrimental effects of patching until they can access such care.

Partial patches are tailored to the patient's particular deficit and should encourage recovery. As discussed earlier, binasal patches applied to the patient's spectacles allow for a full field of vision while eliminating diplopia. They are a particularly good patching method for treatment of esotropia and may enhance peripheral awareness while encouraging abduction. If the esotropia is unilateral, a single patch may be applied to the nasal portion of the patient's spectacles over the nondeviating eye. This technique encourages abduction of the esotropic eye as patients must either abduct that eye or turn their head to view in the visual field ipsilateral to the deviating eye. Binasal patches may also be used on therapy glasses for CN III palsy during safe mobility exercises for several hours daily during which the patient scans across the patch. Scanning like this causes the ground to jump upward and downward and encourages marked reduction of the vertical component of the CN III palsy in some patients. Exotropic deviations may sometimes be treated with translucent bitemporal patches. Thus, each eye must adduct to view in the contralateral field. However, bitemporal patches limit peripheral vision and are not recommended for long-term application or during mobility. For patients who fuse in some fields of gaze but have noncomitant strabismic deviations, partial patches may be applied to a portion of one spectacle lens to occlude only the diplopic field of gaze, allowing for fusion most of the time. At the same time, vision therapy should be applied to expand the field of comfortable binocular vision.

Partial patches may be as inexpensive as a piece of translucent tape applied to the patient's spectacle lenses. Cling patches* are also available commercially. These patches, which stick to the lenses electrostatically, may be easily removed for therapy and reapplied. These also come in varying densities to degrade visual acuity to approximately 20/100, 20/200, or 20/400. The less dense patches enhance patient acceptance because they are, cosmetically, quite good and can hardly be discerned on the spectacle lenses by outside observers. Binasal, bitemporal, and partial patching may not work well for persons with various types of field defects.

* Cling Patch: Available from Bernell Corporation, Mishawaka, IN, www.bernell.com, and Fresnel Prism and Lens Co. Bloomington, MN, www.fresnel-prism.com

Because most TBI patients with secondary strabismus had normal fusion prior to their injury, their prognosis is good for recovering fusion even if one or more muscles are palsied. Even in apparent paresis of the muscle, recovery can occur although the prognosis is more guarded. If a horror fusionis–like response is elicited on initial testing, peripheral fusion techniques emphasizing depth and SILO (see following text) may be used until the patient is able to fuse more central targets. *Antisuppression therapy should not be used on these patients until there is evidence of their ability to attain central fusion as there is a strong possibility of creating intractable diplopia where there previously was none.*

Suppression

Suppression is the ability to diminish or eliminate the central vision originating from one eye to avoid diplopia. In children, it may lead to development of amblyopia in a unilaterally suppressed eye. Once suppression develops, antisuppression therapies must be applied in order to continue with fusional training.

Suppression may be considered either a blessing or a curse, depending on the goal of rehabilitation. If the goal is to restore central fusion with all of the fine motor and stereoscopic advantages that come with it, then suppression is to be avoided through proper application of prisms, patching, or early application of vision therapy. If spontaneous resolution and 3 months of intensive vision therapy show no progress at all toward fusion, then perhaps encouraging suppression to develop may be the most effective way of avoiding diplopia. Antisuppression techniques should not be applied in post-TBI strabismus until there is evidence that the patient can attain and sustain fusion.

If the patient cannot learn to successfully fuse or suppress, then a monovision refractive correction may be prescribed in which the spectacle or contact lens for one eye is set for near work and the other lens is set for distance clarity. This creates one clear image at each distance so that, with practice, the patient learns to easily attend to the clear image, giving a stable referent at each distance. There is a small confusion area approximately 4 feet from the patient where the images are approximately the same clarity with this technique.

DECREASED VISUAL ACUITY

TBI patients with decreased visual acuity that cannot be improved by refractive means or increased contrast will generally profit from standard low vision rehabilitation techniques. Unfortunately, the prospect of accepting their limitations and working hard to learn to use the remaining vision in the most efficient manner possible is not as motivating as the prospect of performing other types of therapy to recover lost visual function. This makes low vision rehabilitation a less positive experience for many patients.

Numerous small telescopes have been developed for magnification of distant objects. These may be hand-held for stationary viewing or for spotting and identification. Increased magnification results in reduced visual field. Therefore, telescopes used only for spotting and identification will generally have higher magnification than telescopes used for distance viewing. Telescopes may also be mounted in the top portion of a spectacle lens for frequent spot reference during such tasks as driving and note taking. A slight downward tilt of the head allows access to the telescope.

For near point tasks, aids range from high-powered convex lenses for near point work, allowing the patient to hold reading material closer, to video enhancement of images via closed circuit television. Bar magnifiers may assist low visual acuity patients in keeping their place during reading. Digital or optical magnifiers that are hand held or stand-mounted for stability are also frequently used.

One of the difficulties in prescribing for the patient with moderately reduced acuity (≤ 20/100) is that many magnifying techniques will slow the process of reading. One must judge whether the patient can be rehabilitated with convex lenses and proper training or whether a magnifier will be of greater assistance. Trial and error to find the correction with which the patient is most comfortable will be a large part of the decision.

DECREASED CONTRAST SENSITIVITY

Contrast sensitivity is the ability to discriminate differences in luminance between adjacent areas. Low-contrast situations occur in fog, darkness, and when viewing through media opacities in the eye, such as cataracts. Reduced contrast sensitivity should be suspected when patients with good visual acuity complain of not seeing well. Neural damage in the visual system may also cause poor contrast sensitivity.[120] Damage to the magno system results in a reduction of contrast sensitivity for middle to low spatial frequency (larger contours). Damage to the parvo system results in loss of contrast sensitivity in detailed targets and may result in decreased visual acuity. Patients with diminished contrast sensitivity in the high frequency range resulting in decreased visual acuity may find magnifying low vision aids helpful. Those with diminished contrast sensitivity for middle to low spatial frequencies are not helped by magnification. Printed material for these patients should be good quality and high contrast. In well-lit conditions, contrast-enhancing tints (usually yellow to amber tints that screen out blue light) or overlays may be used. The selection of tint is usually based on the patient's subjective assessment of the quality of their vision. The Cerium Intuitive Colorimeter* is an instrument that allows presentation of colored wavelength filters, which can be tested through the spectrum of hues, varying the saturation and brightness to

* Cerium Intuitive Colorimeter, available from Cerium Optical Products, Tenterden, Kent, England www.ceriumoptical.com/vistech/colorimetry.aspx

find the lens tint that provides maximal comfort, efficiency, or contrast.

VISUAL FIELD LOSS

Many patients with TBI have resultant visual field loss. Knowledge of visual field defects is important in helping patients adjust their behavior. It is also important for other rehabilitative therapists working with the patient to adjust their therapy, taking the field defect into account. Field defects may be either absolute, with which there is no sensation of light or movement from within the scotoma, or relative, with which brighter, larger, or moving stimuli may still be sensed within the scotoma. Assessment may range from simple confrontation testing to kinetic fields, such as tangent screen or Goldmann perimetry, to automated perimetry with a fixation monitor. Each has advantages and drawbacks. Confrontation testing can be done with no special equipment on patients who are unable to sit as required for the other tests. It gives a gross assessment of the extent of the visual field in each direction with each eye. However, it will not reveal scotomas within those boundaries. Kinetic perimetry testing allows the examiner to very closely map small scotomas and islands of vision within the field, which may not be mapped well on an automated perimeter that presents test points in a predetermined pattern, and may give an expanded field due to the movement perception as compared to static perimetry. Automated perimeters with fixation monitoring give a relatively reliable measurement against which one may chart change in the visual field through repeated measures across time. However, the testing is often lengthy, taxing both posture and attention. Although for the general population, a 30° automated visual field has become standard of care, in patients with brain injury, a 60° field frequently gives a much better understanding of the patient's visual world. Further, one should remember the peripheral crescents that may be spared fall outside of even the 60° field, so if a patient presents with extremely constricted visual fields but navigates well, confrontation testing should be done to attempt to discover whether they are using blindsight or whether they have a spared peripheral crescent.

Probably the most common visual field defect necessitating rehabilitative services is homonymous hemianopia. Rehabilitation has mainly been concentrated on recognizing the field defect and working on compensatory scanning patterns as well as prism devices to allow more peripheral areas of the scotoma to be viewed with smaller excursions of the head or eyes. Patients with hemianopia may also have mild balance difficulties (with their center of gravity shifted toward the blind field).[121] Yoked prism (discussed later) may be helpful in reestablishing balance.

Compensatory visual search into the scotomatous field is found to expand as a result of training, and these gains remain stable over time. Patients with hemianopic field defects who do not receive training do not tend to use adaptive search strategies.[122] Mirrors can be mounted on spectacle lenses,[123] but this technology is not much used anymore as it is cumbersome. Recently, Dr. Tom Politzer has developed a half-silvered mirror that can be positioned at an angle in front of the patient's spectacle lens and viewed through, superimposing the blind field on top of the sighted field. The patient learns to sort the superimposed scenes into right and left fields.[124] More commonly, Fresnel prisms with their apices toward the pupil are added in the peripheral portion of the lens in the scotomatous field(s).[125] These devices move the images that fall in the periphery of the scotomatous field closer to the center of vision. These techniques enhance peripheral awareness because it is easier to view farther into the scotomatous field without head movement, and having the device applied to the spectacles serves as a reminder to do so. Considerable training and motivation are required for successful application of these devices as, when one scans into binocularly applied peripheral prism, the visual world jumps. If the prism is applied monocularly, then patients are diplopic while scanning into the prism and must turn their heads to fixate the object of interest singly after locating it. Rather than using Fresnel prisms, the prism may be ground with patients' spectacle prescription and mounted into their spectacle lens, reducing the optical blur induced by the Fresnel-type prism. This prism system was developed and researched by Dr. Daniel Gottlieb. Limited visual field recovery has been reported in some patients with this type of peripheral prism system applied monocularly,[77] perhaps from reallocation of cortical receptive fields. For patients with severe visual field constriction, the prism technique may be used in all affected fields.[126]

Peli[127] recommends application of horizontal strips of Fresnel prism (typically 40 pd) placed (base toward the visual field defect) superiorly and inferiorly across the lens on the side of the field defect; for a left hemianopia, one would place the prism strips on the left lens. Peli argues that this creates peripheral diplopia, which is easier to adapt to than a peripheral prism that one scans into, and it cues attention to the unsighted visual field without regard to the lateral position of the eyes. In monocular patients or patients who have difficulty with mobility, it may be beneficial to place Peli prisms superiorly only so that the prism does not interfere with vision for mobility. All of the peripheral prism systems are useful tools. Each requires adaptation and training. Various patients will prefer one over the other. Peli prisms may also be useful in cases of visual spatial neglect (see the following) as there are no eye movements necessary to impose the neglected field on the attended field. Stick-on Fresnel prisms can be used for both the Gottlieb and Peli-style prisms. They have the advantage of being inexpensive for trial but degrade over time. Lenses with prism buttons with the patient's refraction ground in and fixed into the spectacle lens are available from Gottlieb's Rekindle group.* Chadwick optical† supplies prisms set into the spectacle lenses for both the Gottlieb and Peli-style prism applications.

* Gottlieb Rekindle Vision, John's Creek, GA. www.gottliebvisiongroup.com/rekindle.html

† Chadwick Optical, Soudertown, PA, www.chadwickoptical.com

Field expanders or reverse telescopes may be helpful in occasional sighting for orientation as when entering a room or locating objects on a table. Distortion and minification when viewing through field expanders make them difficult to use, and again, considerable training and motivation are required.[128]

Perceptual speed and perceptual span, often trained with tachistoscopic techniques, are also important. During mobility, the patient with visual field loss must make more fixations to cover the necessary visual expanse. Perceptual speed and span are also important for reading as any visual field loss that approaches the midline will tend to slow the reading process. Patients with left field loss may not see the beginnings of longer words and misread them as similar words. They also have difficulty returning to the beginning of the next line. The simplest technique for remediating this problem is to keep a finger at the beginning of the next line down or use an L-shaped marker that marks the line being read and has a bright flag at the beginning of the line to indicate the position of the beginning of the line. Typoscopes or rulers may also be helpful. A contrasting strip of ribbon placed vertically along the left margin is a simple, effective technique. Patients with right hemianopias lose the preview information that allows them to judge the placement of the next saccade and guess at the content of the next word. They also have difficulty judging where to return at the end of a line of print and will often return to the next line too early. A finger, hand, or strip of ribbon held at the end of the line serves as an easy marker. These patients may do better reading upside down or rotating the text 90° and reading vertically so that they can preview the text coming up in their sound visual field.[129] Although this may be more cumbersome initially, vertical or upside down reading improves with time, and the left-to-right reading will always be impaired due to lack of peripheral vision guiding the saccade to the next word. Most patients are more comfortable reading toward themselves (rotating the text 90° counterclockwise) even though this may place the next line in their blind field.

There have been reports in the literature of some partial resolution of hemianopia through training with lit targets moving from the scotoma toward the intact visual field and scanning into the scotoma.[76,130] These findings have been questioned by Balliet et al.,[131] who were unable to replicate findings of recovery by training with lit targets. They bring up valid concerns regarding this controversial issue. However, Balliet et al. used smaller targets in their training than were used in the original studies because the smaller target led to less intrasubject variability. In therapy, variable responses may be the hallmark of recovery. In their desire for scientific reproducibility, Balliet et al. may have thrown away the therapeutic effect. Kerkhoff et al.,[76] in a study that had positive results, used a three-step training procedure which included 1) performing large saccades into the blind field, 2) improving visual search on projected slides, and 3) transfer of both to activities of daily living. With this procedure, they were training skills that the patient needed to acquire, and partial resolution of the scotoma seemed to be an additional gift for some of their patients. More recently, computerized systems that present stimuli in the blind field have been marketed for visual restitution of homonymous visual field deficits. The evidence demonstrates no more visual field recovery with these systems than with scanning prism systems.[132]

BLINDSIGHT

An interesting phenomenon that occurs in some patients with large areas of visual field loss from lesions to primary cortex is blindsight. Patients with blindsight are not consciously aware of vision in the "blind" field. However, they are able to report, at levels well above chance, such things as direction of movement and on forced choice "guessing" can discriminate such things as color, location, and sometimes, shape. They consistently deny being able to "see" objects, but may navigate obstacle courses, avoiding objects in their path. Subcortical visual pathways have been implicated previously (reviewed by Stoerig and Cowey[133]), including those to superior colliculus, inferior pulvinar, and the koniocellular layers of the dLGN. Further, functional neuroimaging has shown that cortical areas in the ventral stream can respond to object stimuli presented to the blind field in blindsight-trained patients. Bridge et al.[134] have demonstrated, using diffusion-weighted MRI tractography, a direct ipsilateral pathway between the lateral geniculate nucleus to middle temporal area (MT/V5) without passing through the "primary" visual cortex. Such tracts were reported earlier in the macaque by Sincich et al.[135] Both Bridge et al. and Sincich et al. hypothesize that this tract may provide for visual detection of moving stimuli following destruction of the primary cortex. Further, in a patient who had damage to the primary visual cortex at age 8, Bridge et al. demonstrated tracts between visual areas that did not exist in the control subjects. The implication is that using alternative brain areas for processing information following cortical damage (at least in childhood) may enhance other connections or establish new connections. There have been multiple reports of training blindsight. For example, Chokron et al.[136] trained nine patients with unilateral occipital damage for 22 weeks, presenting forced choice visual tasks, such as pointing to visual targets, letter recognition and identification, visual comparison between the two hemifields, and target localization. All patients improved on blindsight tasks following training, and eight of the nine patients showed enlargement of their visual field on automated perimetry.

PHOTOPHOBIA

Photophobia (i.e., extreme light sensitivity) is a common aftereffect of head trauma.[137] Jackowski,[138] using dark adaptation studies, has demonstrated damage to rod-mediated visual mechanisms in brain injury patients with significant photophobia even though they seldom complain of their night vision being reduced. The rods (i.e., dim light vision receptors) mainly feed into the magno visual subsystem. Cone-mediated visual mechanisms were also damaged in these patients, but these deficits were small in comparison to the rod-mediated visual loss. The cones (i.e., daylight vision

receptors) mainly feed into the parvo pathway. The magno and parvo pathways are mutually inhibitory. Jackowski has hypothesized from her findings that damage to the rod system, or magno pathway, disinhibits the cone, or parvo, pathway, causing this bright light–sensing pathway to be overly responsive; this mechanism may be the cause of posttraumatic photophobia in many patients.

Patients who have posttraumatic binocular disorders or pupil dilation of one or both eyes may also complain of photophobia. Successful treatment of the binocular dysfunction will lessen the photophobia in cases in which this is the primary cause. Otherwise, photophobia may be handled with any number of tints in the patient's spectacle lenses, the color and density of which are mainly prescribed for subjective comfort; see Stern[139] for additional information on specific tints. Patients with extreme photophobia who also experience imbalance and/or visual confusion in visually busy spaces frequently benefit from indoor tints determined by Intuitive Colorimeter testing. These should not be prescribed with maximal brightness attenuation even if the patient prefers this as they will be too dark for indoor wear.

Photochromic lenses that darken in sunlight and lighten indoors may be helpful although they do not darken well for driving applications. Although eye protection from ultraviolet radiation should be a consideration for everyone, it is even more important to incorporate ultraviolet protection into tinted lenses for patients with mydriatic pupils. In extreme cases of mydriasis, it is sometimes possible to prescribe an opaque custom contact lens with a small transparent pupil to decrease the light entering the eye. However, often, patients with mydriatic pupils have dry eyes, and contact lenses would be contraindicated.

INTOLERANCE OF BUSY SPACES

Inability to tolerate visually busy or patterned spaces, such as crowded stores or patterned hotel carpets, is a symptom rather than a diagnosis. This symptom is elusive in the literature. However, it seems important to include it in this chapter because it is so common following TBI, debilitating, and not generally elicited in a history unless one asks the question directly. It no doubt has multiple etiologies but is being discussed here under reception because at least some of those etiologies are receptive. Clinically, it may be associated with PTVS, small vertical phorias, or possibly difficulty with optic flow or magno–parvo imbalances. Remediating any residual binocular dysfunction, especially small vertical phorias, binasal patches, base-in prism, or Intuitive Colorimeter lens tinting may provide significant or complete relief to many patients with this symptom.

Assessment and rehabilitation of perception/integration/attention

LOCALIZATION AND SPATIAL VISION

There is little information on effects of brain injury on the magno pathway until it reaches the cortex. However, it is known that the large axon diameter of the magno cells makes them more vulnerable to various types of damage as in glaucoma and Alzheimer's disease.[93] Disorders of motion perception are rare.[140] Indeed, studies in monkeys show that a lesion in the MT area produces disorders of motion perception, but that most of these disappear within a few days, presumably because the function is taken over by redundant pathways. Damage to the posterior cerebral cortex often results in spatial inattention to the contralateral visual field known as *unilateral spatial neglect* (USN) or *visual–spatial neglect* (VSN) discussed subsequently.

A number of reception dysfunctions affect perception of spatial localization and orientation. For instance, we use the feedback from our vergence system to assist us in judging distance. If our eyes are more converged, then the target we are fixating is seen as closer. In persons with good binocularity, this effect, called *smaller in*, *larger out* (SILO),[141] can be demonstrated by the use of prisms. If one fixates a target and places base-out prism in front of the eyes, the images of the target are moved in a convergent direction, and the eyes must converge in order to avoid diplopia. The target will be perceived as having moved *in* toward the observer and will appear smaller than before. Size constancy dictates that objects get larger as they come closer but, because the target has not really moved, the image size on the retina remains unchanged. Therefore, because the vergence system says the object is closer, but the image size remains unchanged, the interpretation must be that the object is now smaller. Base-in prism produces the opposite effect: when the eyes diverge, the object appears to move out away from the observer and appears larger. Due to the roles of accommodation and convergence in depth perception,[101] sudden onset of dysfunctions in accommodation or convergence secondary to TBI can make objects appear closer or farther away than they actually are, effectively collapsing or expanding visual space.

Conversely, feedback from the cortical and subcortical spatial processors affects the vergence system. For example, one type of convergence is driven strictly by proximity to an object; targets close to the face make us converge even though we may be viewing through an optical system set at infinity. The TBI patient with a primary visuospatial disturbance will often have inaccurate eye pointing.

Feedback in visuospatial processing runs both ways from the binocular system to visuospatial processors and from visuospatial processors to the binocular system. Therefore, the most effective therapy for disorders of spatial perception in depth must take into account the binocular response. Similarly, the most effective treatment for eye teaming will, often, concentrate not only on achieving the correct motor response, but also on creating correct spatial judgments, which can be used to guide the motor response.[142]

Other difficulties in spatial organization may be reflected in inability to properly localize objects in relation to oneself. Egocentric "midline shifts" of varied etiologies have been noted in patients following brain injury. These shifts in midline perception can cause shifts in posture and weight

distribution, which may cause difficulty with balance and gait. They may also affect eye–hand coordination. Tests used to detect egocentric visual midline shifts include line bisection tasks[143,144] and, more commonly, subjective judgment by the patient of when a wand or pencil, held in a vertical orientation and moved laterally, is directly on the horizontal midline (i.e., in front of the nose).[16] Other, more elaborate tests that will give more complete information on the spatial distortion are described in the literature.[145] Visual field defects, hemifield visual neglect, disruption of the midbrain ambient visual system, tonic ocular–motor imbalance, and imbalances in extraocular proprioception or efferent copy commands to the extraocular muscles are all possible causes of midline shift. As described by DeRenzi,[146] tonic ocular–motor imbalance is an increased tone in the muscles turning the eyes to the side contralateral to the lesion. During routine testing, it is masked by the fixation mechanism, but it can be elicited by having the patient attempt to look straight ahead in darkness. During development, we learn to maintain position constancy of objects in spite of eye movements by comparing the efferent copy (commands going out to the eye muscles) and proprioceptive information received from the eye muscles, with the movement of the retinal image.[107] As the eyes, extraocular muscles, and separation between the eyes grow and change, slow adjustments in these systems take place. However, in TBI, a sudden change in any one of these systems may occur, changing the perceived location of objects in relation to ourselves.

Therapy for spatial distortions may include therapy for accommodative and convergence disorders as described previously with special emphasis on development of SILO and spatial localization. Lenses and prisms may be applied in either a compensatory manner or for therapy purposes. Spatial and postural effects of these optical devices are thoroughly reviewed by Press.[147] Padula[11] advocates use of small amounts of base-in prism in order to facilitate reorganization of the ambient system by reducing stress on the peripheral fusional system in cases of exophoria. Yoked prisms (i.e., equal amounts of prism in front of each eye with both bases in the same direction: up, down, right, or left) are an effective intervention for many cases of egocentric midline shift. These prisms move images of the surrounds in the direction of the apex of the prism for both eyes. Low amounts of yoked prism may be used in a compensatory manner[35,148] to shift images of objects that belong on the visual midline to the recently misplaced perceived visual center; this relieves the perceptual mismatch between what actually *is* and what is perceived, often restoring balance, normal gait, and the ability to move about easily in the world.

Large amounts of yoked prism, such as 15 prism diopters, may be used in therapy to force problem solving and increase flexibility in the sensorimotor system. Activities, such as walking or tapping a swinging ball, while wearing these prisms involve recalibration and integration of vestibular, proprioceptive, kinesthetic, and extraocular efferent copy systems. This is an extremely effective technique for disrupting habitual patterns in patients who have been unresponsive to more instrument-based therapies so that, with guidance, they can reorganize their visual–motor system in a more adaptive manner. Therapeutically, yoked prisms are only worn for periods extending from a few minutes to a few hours. It is important to note that, in an observer with a normal visual system, prism adaptation would be expected to occur with long-term wear. Presumably, those individuals who experience a long-term compensatory effect wearing yoked prism full time have visual dysfunction that precludes prism adaptation to this prescription. This reasoning makes sense in that if these patients had been able to do the sort of reorganization that prism adaptation requires, they would probably not have sustained an egocentric visual midline shift.

VISUAL–SPATIAL NEGLECT

VSN, sometimes termed *visual hemi-inattention* when it affects an entire hemifield, is a phenomenon with which a portion of space is simply unattended as if nothing existed there. On a visual field test, it may appear as a hemianopia. But, worse, patients are unaware of the defect. This makes them more prone to accident and more difficult to rehabilitate than the hemianope without neglect. When neglect affects only the visual system, it may easily be mistaken for hemianopia and, indeed, often coexists with true hemianopia. VSN is frequently concomitant with neglect of other senses, such as audition, as well as motor neglect, in which case the entire phenomenon is termed USN or *unilateral hemi-inattention*. Split-brain research[149] has provided evidence that the right hemisphere allocates attention to both visual fields, and the left hemisphere allocates attention to only the contralateral field (Figure 26.6). This finding in split-brain patients suggests that the right hemisphere allocation of attention to the right visual field is probably mediated through subcortical mechanisms. It may also help explain why most cases of overt neglect are secondary to right brain damage.

Although VSN of an entire hemispace is easily mistaken for hemianopia, the mechanisms and damaged brain substrates underlying VSN are quite different from hemianopia. Hemianopia is a sensory loss, with which the damaged neural substrates are in the postchiasmal visual pathway up to and including the primary visual cortex. VSN is a perceptual deficit, with which the neural substrates necessary for sight are intact, but the visual substrates or pathways necessary to attend to or perceive the sensory input are not. VSN may best be thought of as a competitive process, with which gradients of attention are distributed across the two halves of the visual field and often also in a superior–inferior direction. The more stimuli there are on the more attended side, the denser the neglect for the less attended side becomes. VSN may involve, separately or concurrently, the patient's own body (personal neglect), the space within arm's reach (peripersonal neglect), or the space beyond arm's reach (distant neglect). Object perception may be involved such that only half of the object is perceived. VSN should be thought of as a syndrome that involves one or more multiple neural substrates rather than a unitary disorder.[150]

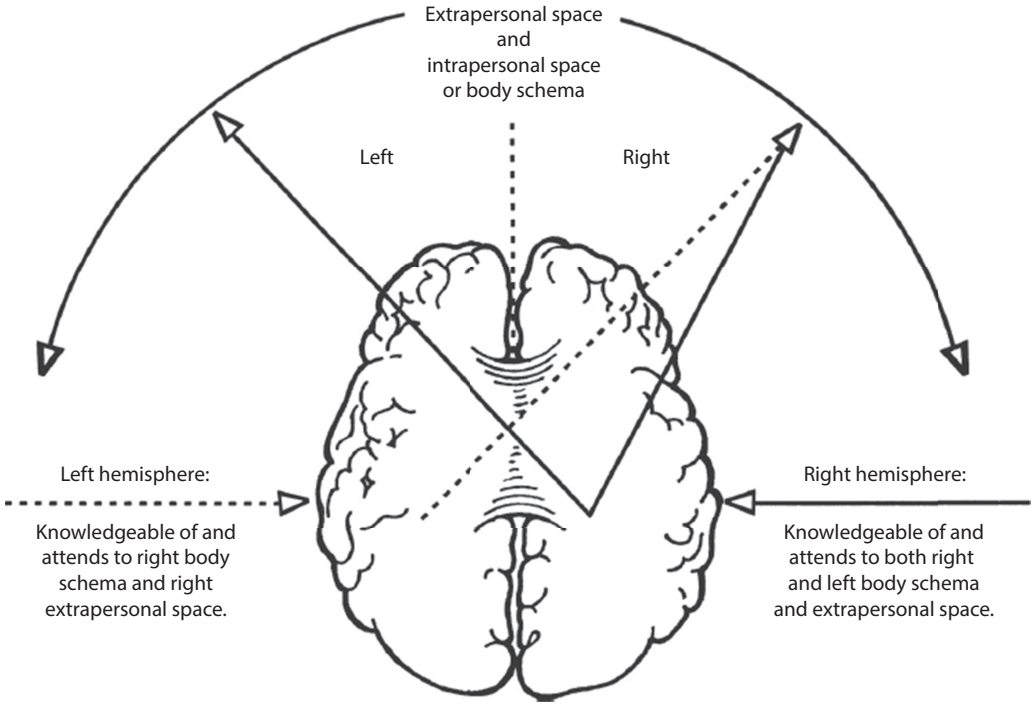

Figure 26.6 Allocation of spatial attention by the cortical hemispheres. The right hemisphere allocates spatial attention to both the right and left visual fields whereas the left hemisphere allocates attention only to the right visual field. Thus, USN of the left visual field (following right brain damage) is considerably more pronounced and easily observed than USN of the right visual field. (Adapted from Moore, J. C. and Warren, M., *Effect of Visual Impairment on Postural and Motor Control following Adult Brain Injury*, Continuing education workbook by visABILITIES Rehab Services, Inc.: www.visabilities .com. With permission from J. C. Moore.)

The neural substrates for neglect lie in multiple centers of the brain. The posterior parietal cortex, temporoparietal junction, and portions of the dorsolateral frontal lobes as well as the parietofrontal pathways, the caudate portion of the superior temporal gyrus, the cingulate gyrus of the limbic system, and subcortical areas, such as the pulvinar in the thalamus and the putamen and caudate nucleus in the basal ganglia have all been implicated in neglect.[10,151–153]

Various tests, including drawing, line, or other cancellation tests, pointing to objects scattered around the room, reading a newspaper article, and line bisection, have been developed to determine the presence of VSN. VSN may vary in degree and appear on some tests but not others.[154] Inattention may also be differentially distributed along the vertical meridian of the neglected field.[144,155] As reviewed by Kerkhoff et al.,[76] during line bisection tasks, patients with neglect typically transect the line off to the side contralateral to the field defect. Patients with hemianopia generally do the opposite, deviating in the direction of the scotoma. Patients with both are more likely to bisect the line. Compared to patients with hemianopia without VSN, patients with VSN have even more abnormal scan paths when viewing simple figures and with fewer excursions into the blind field.[156]

Clinically, three considerations are important during therapy for VSN (N. W. Margolis, personal communication). First, the patient must be made aware of the condition. Second, compensatory strategies, such as scanning and reading strategies, should be taught. Last, these strategies must be generalized to both static, predictable stimuli (i.e., those encountered in reading or walking down a familiar corridor) and to dynamic, unpredictable stimuli (i.e., encountered in new environments). Margolis[157] and Margolis and Suter[158] review treatments for VSN. However, a singular therapy is worth mentioning here. Rosetti et al.[159] reported that large amounts of yoked prism (15 to 20 pd) with the bases oriented into the neglected field worn during visual–motor activities created immediate improvement in VSN that lasted hours or days following this therapy. Clinical experience shows that the results can be dramatic in some patients when used in conjunction with other standard VSN therapies. In applying the prism adaptation paradigm, one must be aware that Gossmann et al.[160] demonstrated that, although the improvement in egocentric VSN can be quite impressive with improved trunk, head, and eye orientation as well as improved cancellation tasks, there was no improvement in allocentric VSN, such as line bisection in their patient group. Gordon et al.[161] present a three-step program for remediation of perceptual deficits in patients with right brain damage. Step 1 is basic scanning training. Step 2 is somatosensory awareness and horizontal size estimation, and Step 3 is complex visual perception training combined with left-to-right visual scanning within these tasks. They present evidence that, with extensive training, these functions generalize to daily living. Gianutsos[83]

reviews the literature on perceptual rehabilitation in USN and concludes that, overall, the efficacy of therapeutic intervention is supported. However, studies of solely microcomputer-based scanning therapy have not been shown to generalize.[162,163]

OBJECT PERCEPTION

The visual percept we construct from sensory signals supercedes even the concrete sensation of touch. For instance, if an object (i.e., a square of plastic) is viewed through a minifying lens and is simultaneously manipulated by the hand (with the hand covered so that it cannot be used as a visual cue), the observer reports the square as being smaller than the real square. This is true whether the method of report is visual (i.e., picking a matching square out of a range of squares of various sizes), visual and tactile (i.e., drawing the square to size), or, surprisingly, tactile (i.e., picking a matching square by touch alone).[164]

It has been suggested that, visually, we construct perceptual objects via a two-step process.[165] First, preattentive data-driven filtering produces shapes and registers their features as in reception. Then, focal attention is used to select a spatial location and integrate the features registered there into a perceptual object. This is analogous to figure–ground organization and should be concept-driven processing rather than data- or sensation-driven. Evidence arguing for this feature integration theory comes from the way that stabilized retinal images fade feature by feature rather than in small random parts. Principles at work during the second integration stage may be the Gestalt principles of proximity, good continuation, similarity, closure, and pragnanz (i.e., simplicity, regularity, or symmetry) or local versus global processing. In addition to integrating visual features, object perception includes cross-modality integration (i.e., integrating auditory, tactile, and olfactory sensations with visual information to complete the perceptual object). Spatial orientation, both the ability to process the orientation of external objects (extrapersonal orientation) and the ability to process the orientation of ourselves with regard to other objects (personal orientation), is discussed here because the treatment modalities are generally more similar to those used with object perception than other spatial dysfunctions. Personal orientation may be supported by the frontal lobe (particularly in the left hemisphere); extrapersonal orientation may be supported by the dorsal "where" pathway, particularly the right posterior parietal area.

Assessment and treatment of perceptual/integrative vision must take into account dysfunctions in reception. Multiple tests, with some redundancy, are necessary to differentially diagnose perceptual dysfunction of the visual system. For instance, copy-form tests are useful and may tell you something about spatial organization, but if the forms are poorly reproduced, you do not know whether this is due to difficulties in reception, perception, visual–motor integration, or fine motor coordination. One must have a battery of tests that probe perceptual functions, such as figure–ground discrimination, closure, and spatial organization, as well as cross-modality and visual–motor integrative functions from different perspectives using different modalities. Gianutsos[83] reviewed many of the available perceptual tests. Groffman provides an updated battery of tests.[166] For another sample test battery, see Aksionoff and Falk.[167] The perceptual workup will generally take 2 to 3 hours to administer and may need to be broken up into multiple sessions for TBI patients who fatigue easily.

During therapy, the patient and therapist must constantly keep in mind that it is the process, not the final answer, that is important. When possible, the strategies patients are using to solve a particular problem in therapy should be discussed. This creates awareness of the process and insight for the therapist and provides the opportunity for the therapist to suggest modifications in the patient's problem-solving strategy. As reviewed by Groffman,[168] perceptual therapies may be considered as falling into a number of treatment modalities: 1) motor activities; 2) manipulatives; 3) instruments; 4) vision therapy; 5) lens therapy; 6) auditory therapy; 7) workbooks, toys, and games; and 8) computers. The modality is tailored to fit the level and perceptual deficit of the patient.

Although gross motor activities applied in vision therapy have often been criticized by professionals who are not involved in therapy, gross motor activities are frequently necessary in vision rehabilitation to create more optimal support for the visual system. The eyes and visual system do not exist in isolation; the eyes are horizontally displaced from each other in the head, and the biomechanics are such that they are intended to work with a horizontal disparity in relation to gravity. Tilting the head induces ocular torsion. Gross motor activities are also used for creating visual–proprioceptive and visual–kinesthetic matches in ambient space. Vision is dominant over touch in the normal visual system. However, in therapy, proprioceptive and kinesthetic feedback can help teach veridical visual perception. In the rehabilitation setting, many therapeutic activities with these two goals can be taken over by physical or occupational therapists.

Manipulatives are objects that can be used on the tabletop so that they can be handled, rotated, rearranged, and examined in a very concrete way. They allow for learning higher-order visual concepts, such as visual discrimination, form perception, and spatial orientation and organization, with very concrete tools. These include blocks and puzzles specifically designed to teach perceptual skills. Other common examples of manipulatives are flannel boards (used with felt shapes of varied sizes and colors), geo boards (i.e., boards with evenly spaced pegs on which designs are made by stretching rubber bands between the pegs), or Peg-Boards™, which can be used for reproducing patterns with or without rotations in orientation. Manipulatives also provide excellent eye–hand coordination activity.

A variety of instruments have been developed for visual–perceptual training. Instrument techniques are varied and seem to provide additional motivation to many patients. An example would be adjustable-speed tachistoscopes

(computerized or mechanical), which are used to increase visual perceptual speed and span, as well as visual attention and short-term memory. Tachistoscope targets may vary from abstract geometric forms to be copied to digit strings or words. They are also useful to demonstrate VSN or hemifield loss to the patient as, without time to scan, they will only see the portion of the word presented in the intact field.

Application of vision therapy to remediate receptive dysfunction often involves visual perception—both in spatial organization as discussed previously and in that many fusion tasks require figure–ground discrimination. Lens and prism therapy have already been discussed in terms of shifts in the localization and orientation of local surrounds.

Many workbooks, toys, and games are available in educational supply stores, including popular activities with hidden pictures or words for figure–ground discrimination and form perception. Worksheets with simple, incomplete figures to be completed by the patient may be used for development of closure as well as form perception. These tools also help develop eye–hand coordination. They are generally two-dimensional representations, but have the advantage that, once they understand the process, patients may practice unsupervised with worksheets.

With most of the above activities, the understanding of the visual goals, experience, and creativity of the therapist are key to the success of therapy. However, through development of computer programs, perceptual therapy has become more accessible and more easily administered by other rehabilitation disciplines, such as occupational therapy. A number of perceptual programs that combine the challenge and motivation of a video game with good perceptual therapy are online for free or commercially available. Computer therapy generally requires the ability to manipulate a joystick or press a limited number of response keys. For patients having motor control problems, this may be easier than using workbooks or manipulatives.

Visual agnosias

Agnosia is the inability to recognize objects visually. Object recognition may be apperceptive, with which the perception of the object is faulty, or associative, with which the object is perceived correctly but cannot be associated with prior memories or past experience.[169] In apperceptive agnosia, patients might not be able to match similar objects, draw or copy objects or shapes, or name objects by sight. However, if allowed to use tactile input, they could both name and match the object as well as describe its function. Apperceptive agnosia is rare and is associated with diffuse cerebral damage of the occipital lobes and surrounding areas.

In associative agnosia, objects and shapes can be matched, but patients are unable to associate them with past experience or function. For instance, they may be able to draw a key that is placed before them, but be unable to name it or describe its function. When allowed to handle the key, they could both name it and relate that it is used to unlock a door. Associative agnosias can be surprisingly specific. The more common types of agnosia include object agnosia, prosopagnosia (i.e., inability to recognize familiar faces), and color agnosia.

Diagnosis of visual agnosias is important in deciding the proper course of treatment: therapy or compensation. Associative agnosias may be due to lesions in the pathway that connect the visual "what" pathway with memory areas. De Haan, Young, and Newcombe[170] have shown that covert recognition of objects and faces may exist in the absence of overt recognition. They suggest that this may provide a foundation for rehabilitation. Sergent and Poncet[171] report some restoration of overt face recognition under specific circumstances in one patient. Although, in some cases, restoration of function may be possible, therapy to directly address the agnosia is likely to be a long process, and success is not guaranteed. Compensatory strategies, as for low vision or blind patients, may be the best alternative for immediate management of agnosia.

Alexia

An important part of text recognition is the decoding of visual percepts into language. Interruption of visual pathways at the left angular gyrus[172] or splenium[173] prevent this decoding process from occurring, resulting in acquired alexia or inability to read. Most case reports of this dysfunction show some residual reading function. Treatment of alexia using integration strategies and based on the patient's residual reading skills has been successful. Often, a letter-by-letter reading strategy can be employed by these patients, although it severely slows reading. Motor rehearsal, in terms of copying or tracing letters and words, as well as flash card techniques pairing the written with the spoken word have been applied with some success.

A successful strategy employed with one patient is described by Daniel et al.[172] Initially, the patient spelled words aloud from flash cards and, then, said the word (as he recognized the word from auditory spelling). With practice, the patient was able to substitute covert spelling. Continued practice in this manner significantly increased his ability in reading and naming so that he was able to return to work within 4 months postinjury. At the 1-year follow-up, reading was still laborious, but the patient was able to read sufficiently to function in his job.

Assessment and rehabilitation of motor output/behavior

Visually directed motor output includes not only the planning and execution of eye–hand coordination and visually guided movement through space, but also the planning and execution of the next eye movement. As in the model (Figure 26.4), reception affects perception, which affects cognition, and both of the latter affect programming of the next eye movement, feeding back into reception (control of binocularity, eye movements, and fixation). This is a flexible, but closed, loop.

EYES

Most aspects of assessment and rehabilitation of motor output to the eyes have been discussed in the "Assessment and rehabilitation of sensory input/reception" section in this chapter. The rehabilitation already discussed is generally performed in the vision care setting. Some specific exercises may be prescribed for application by occupational therapists in either inpatient or outpatient rehabilitation settings.

In addition to the aspects of ocular–motor and binocular control that have already been discussed, ocular–motor planning and integration with the output controllers to the eyes are involved. Ocular–motor gaze apraxia is the inability to execute purposeful eye movements (reviewed by Roberts[169]). Patients with ocular–motor gaze apraxia may be differentially affected for various stimuli, e.g., unable to change fixation in response to verbal commands or peripheral visual, auditory, or touch stimuli. This may be exploitable in that one may be able to practice saccades to a multimodality stimulus and wean out the intact modality. An activity such as Letter Tracking,* with which one underlines rows of letters until a target letter is reached and then circles the target letter, may allow tactile–proprioceptive feedback to help guide eye movements. Treatment here falls into the realms of neuropsychology, occupational therapy, and vision therapy.

Compensatory strategies should be trained at the same time that remediation is attempted. Many compensatory strategies developed for low vision or the blind may be useful. Other strategies that lessen the necessity of looking in a particular location or reduce the need to scan can also be taught. For instance, moving the television away or using a small screen lessens the need to scan the scene in an organized fashion.

HANDS

Eye–hand coordination will be affected by receptive and perceptual problems as well as by motor planning and integration of percepts with motor output controllers. Mild difficulties that occur developmentally in these areas will often result in clumsiness or difficulty with such tasks as producing clear handwriting. More severe dysfunction is described by two terms: *optic ataxia* and *constructional apraxia*.

Optic ataxia is an inability to visually guide the hand toward an object. Differentiating optic ataxia from primary dysfunctions in motor control can be achieved by having patients touch their index finger on one hand with the index finger on the other. Usually, in optic ataxia, the misreaching occurs for objects in the peripheral field. However, in more severe cases, misreaching will occur for visually fixated objects.[169] For milder cases, training the patient to visually fixate manipulated objects may be all that is required.

Constructional apraxia generally results from lesions of the posterior parietal lobe or the junction between the occipital, parietal, and temporal lobes. It may be due to perceptual deficits, more frequently associated with right hemisphere lesions, or motor function deficits, more frequently associated with left hemisphere lesions. Walsh[174] lists differential effects on drawing that may be used to discriminate between perceptual and motor etiologies. For instance, right hemisphere lesions will tend to result in energetic, scattered, or fragmented drawings with a loss of spatial relations and orientation; left hemisphere involvement tends to result in drawings that are spatially intact and coherent but simplified and laborious, lacking in detail.

Again, treatment here falls into the realms of neuropsychology, occupational therapy, and vision therapy. A multitude of hand–eye coordination activities exists in the literature. For constructional apraxia, the differentiation should be made as to whether it is primarily perceptual or primarily motor, and treatment should emphasize that modality.

BODY

As discussed previously, receptive and perceptual dysfunctions can lead to adoption of head tilts or turns and shifts in posture, creating or complicating problems in balance during standing and walking. Patients are, often, unaware of these postural adjustments and, when asked, will deny any distortion in their percept and usually in their posture even though something as easily noticed as a pronounced head tilt may be present. Testing for binocular dysfunctions and conditions that may contribute to egocentric midline shifts in the vertical and horizontal directions has been discussed. The vision practitioner must take a careful history and specifically ask about difficulty with balance, instability, mobility, etc., as most patients with these symptoms will, often, not bother to tell an eye doctor about these difficulties as they assume the symptoms are unrelated to their eyes.

If a binocular dysfunction exists, the associated postural problems generally resolve as the binocular problem is remediated or when appropriate patching is applied. Treating the binocular difficulty not only relieves the diplopia or intermittent loss of fusion, which can cause patients to adopt compensatory head and body postures, it may also involve teaching patients to reorganize their visual space in which the binocular problem has created distortions.

In the case of an egocentric midline shift, the specific etiology is, often, not diagnosed. Tests for midline shift or observing immediate responses to large amounts of yoked prism may be the extent of the diagnostic procedures. The effects of yoked prism on spatial organization and resultant shifts in posture with a normal visual system are well documented (reviewed by Press[147]). Yoked prisms move the images of the ambient surrounds in the direction of the apex of the prism for both eyes. In the normal visual system, this gives a funhouse effect. It is, initially, rather disturbing during head movements and walking to have the world shifted to the right or left or, seemingly, stretched upward or squashed downward before you. Base-up prism will generally cause wearers to shift their weight backward onto their

* Letter Tracking: Available from Academic Therapy Publications, Novato, CA. www.academictherapy.com

heels; base-down prism generally has the opposite effect, causing the wearer to shift weight forward onto the toes. Sometimes, these prisms may be prescribed to assist the physical therapist in rehabilitation of standing and walking. Often, with TBI patients, yoked prism applied in one lateral direction will create no noticeable difference, and application in the opposite direction will make them unable to walk as they try to balance against the shift in surrounds. This type of behavior is a good indication that yoked prism therapy or compensatory yoked prism in patients' spectacle lenses can help normalize their posture and balance, either by reorienting their egocentric visual midline or by moving the image of the outside world to match their new internal visual midline. Patients who veer in one direction while walking may also benefit. Even without a visual midline shift, yoked prisms used for short therapy periods may be useful in breaking down maladaptive habitual postures that are resistant to treatment.

Similarly, visual interventions may be useful in patients with upper limb hemiparesis although there is not a visual cause. Practicing visual imagery of movement of the paralyzed limb in conjunction with physical and occupational therapy can improve outcomes over therapy alone.[175]

Assessment and rehabilitation of visual thinking/memory (visual cognition)

Visual images may be stored in either analog or verbal storage. Therefore, when attempting to rehabilitate visual thinking and memory, it is important to be sure that the patient is not merely encoding the information verbally, but actually forming the mental image. Unlike visual perception, which is largely a bottom-up process, visual imagery is largely a top-down process. Visual imagery uses visual information that has been previously organized and stored; therefore, it is often possible to use visual imagery even though, after a TBI, visual input and perception may be disordered. Thus, sometimes, it may be trained in parallel with, or even in the absence of, organized visual perception.

Visualization, or the use of visual imagery, has long been considered a useful high-end visual task by therapy-oriented optometrists. Visualization can be used for visual memory enhancement, such as visualizing the spelling of a word, or for spatial relations and spatial organization, for instance, visualizing object rotations or visualizing a map of how to get home from the grocery store. Numerous studies using various biological indices (e.g., electrophysiology, cerebral blood flow, and other types of brain activity imaging) as well as studies of adults with brain damage show that, when internally constructing visual imagery, we may use many of the same visual representations as in constructing visual percepts from sensory input (reviewed by Farah[176] and Kosslyn and Thompson[177]). Techniques based on visual imagery may be used effectively for perceptual therapy for those patients who do not have manipulative abilities, provided that they are effective at using imagery. Problem solving with visual imagery occurs by using visual imagery from both memory and imagination. These are separate skills and are used differently in problem solving.[178]

Visual memory, particularly visual sequential memory, is frequently impaired following TBI. Often, when there is post-TBI memory loss, verbal compensatory strategies are employed, such as list making and writing in a calendar or log. These techniques rely heavily on left hemisphere mechanisms. Rehabilitation of visual memory, which can be built on visual imagery, a heavily right-hemisphere function,[179] can provide supportive memory function and help organize incoming visual information, reducing general confusion.

There are many well-standardized tests that tap visual memory. One such test, which taps short-term visual memory and visual sequential memory, is the Test of Visual Perceptual Skills.[180] An advantage of the Test of Visual Perceptual Skills is that it allows the patient to simply point to the correct answer, minimizing the need to generate complex motor or verbal responses. It also provides separate assessments of visual memory for figures and visual sequential memory, the latter being critical in reading comprehension and in creating order from the visual information received.

One representative technique for practicing visual imagery from memory and improving visual memory is to use flannel boards. The therapist and patient have matching felt forms, such as squares, circles, rectangles, and triangles of varying sizes and colors; each of them also has a flannel board on which to place the forms. The therapist places some of the forms on a flannel board in a spatial or sequential pattern. The patient is instructed to form a mental image of the pattern presented without using words to describe it. Then, the therapist's board is covered and the patient reproduces the pattern on his or her flannel board. As the performance improves, the number of forms is increased, the exposure time is reduced, and the delay between exposure and reproduction is increased in order to encourage transfer to long-term memory. Distracters may be interposed during the delay between exposure and reproduction. Flat, three-dimensional blocks, available commercially in foam or wood, can be used for patients who have difficulty manipulating felt forms.

Using visual imagery from imagination is a separate skill and is used in problem solving. Activities that emphasize this skill would include solving constructional or rotational problems.

SUMMARY

The term *visual rehabilitation* is so broad that it often encompasses the services of neuropsychologists, occupational therapists, and psychotherapists in addition to ophthalmologists and optometrists and specially trained orthoptists, vision therapists, or orientation and mobility specialists. Besides damage to the receptive structures, such as the eye and optic nerve, visual dysfunction may be caused by damage to any lobe of the brain as well as midbrain structures and cranial nerves. Functional deficits include

photophobia, decreased visual acuity or contrast sensitivity, ocular–motor disorders, binocular dysfunction (including strabismus), visual field loss, spatial disorientation, imbalance, unilateral spatial neglect, other visual perceptual disorders, integration disorders, and problems with visually guided motor planning and motor output.

Visual sequelae are quite commonplace, but often overlooked in the TBI patient. Therefore, once the medical or surgical rehabilitation of the visual system is complete, the issue of functional recovery or compensation must be examined. Vision care specialists who provide other patient populations with orthoptic or vision therapy or low vision services will generally be able to adapt many of their techniques to working with the TBI patient. Treatments often must be innovative and coordinated among the various professionals providing rehabilitative services. Visual sequelae to TBI can affect the patient's ability to perform such varied tasks as reading, walking, and driving. Unrehabilitated functional visual deficits can interfere with other therapies and with the patient's ability to perform activities of daily living as well as return to work or school. They may also be a source of emotional turmoil as the patient may experience unexplained feelings of imbalance, spatial distortion, or visual confusion and may be unjustly suspected of malingering.

The neuroanatomy of the visual system is so complex that, in order to provide effective therapy, one must have a working model with which to organize rehabilitation. Such a model is described in Figure 26.4. The major components of the model to be considered in diagnosis and therapy are 1) sensory input/reception, 2) perception/integration, 3) motor output/behavior, and 4) visual thinking/memory. In this model, each component affects the other. Our receptive functions affect perception and survival motor outputs. Our percepts affect our motor planning/output as well as our thinking and memories. Our thinking and memories mediate our perceptions as well as affecting our motor planning and output; motor planning and output determine where our bodies are and how we are going to use our eyes next, mediating receptive function. Carefully planned vision therapy or use of lenses and prisms can intervene in any of these areas in a constructive way or disruptively to break down bad adaptations.

The redundancy of the visual system as well as the flexibility of the visual system—demonstrated by experiments, such as adaptation to inverting prisms, together with clinical experience, such as therapeutic remediation of strabismus and amblyopia in adult—makes recovery of function a reasonable goal for many visual dysfunctions following TBI. Although one cannot always predict which patients will respond to such therapy, it seems inappropriate to offer less if there is a chance of recovery. When therapy is ineffective at restoring function within a reasonable time frame, there are many compensatory devices and strategies that can be applied, for instance, partial patching, prisms, or low vision devices and techniques. Even these should be prescribed with an eye toward maximizing function within the limits set by the patient's condition. The multiple deficits in sensation, speech and language, cognition, behavior, emotional state, and motor control encountered in TBI patients add to the challenge of providing effective vision care and make an interdisciplinary team approach most effective in returning the patient to optimal function.

ILLUSTRATIVE VISUAL CASE STUDIES

Patient J. G.

Patient J. G. was seen for vision evaluation 4 years after sustaining an MTBI when she slipped and hit her head. Since then, she had been unable to read, sew, or do any near work for more than 10 minutes without getting a headache. She also complained of dizziness and photophobia. She had been through vision therapy previously, but on an intermittent basis due to geographic constraints. She was admitted to a postacute, inpatient rehabilitation setting for treatment.

J. G. was diagnosed with accommodative and convergence insufficiencies as well as a saccadic dysfunction. Based on her symptoms and these findings, a working diagnosis of PTVS was indicated. Glasses were prescribed for full-time wear. As J. G. was orthophoric at distance, base-in prism was not prescribed. However, she received a bifocal (in order to compensate for her accommodative insufficiency) with binasal patches (to help reduce her visual confusion and reorient her in space). J. G. reported immediate relief of many symptoms with decreased photophobia and increased ability to do near work while wearing this prescription. Because her stay would be limited and her visual complaints were central to her rehabilitation, J. G. was seen weekly in the optometrist's office for vision therapy. Exercises were prescribed for convergence, accommodation, and saccadic dysfunction, which were administered by occupational therapists daily at the rehabilitation center. J. G. responded well to her prescription, binasal patching, and vision therapy. She simultaneously underwent vestibular therapy with the physical therapists. Within 3 months, the binasal patches were removed from her glasses, and she was able to read and sew as long as she liked (which turned out to be for hours at a time). She continued to wear the glasses full time. The rehabilitation center arranged for her to spend an evening waitressing in a local restaurant (this was her former occupation), and she performed so well that the owner offered her a job. She returned to her home feeling fully rehabilitated and ready to return to her preinjury work and home life.

Two factors may have contributed to J. G.'s dramatic recovery in this case. She was in a rehabilitation setting where she was able to take advantage of coordinated rehabilitation services on a constant, rather than intermittent, basis. Also, placing her in a full-time prescription with binasal patches provided her with consistent, organized, visual input so that she could create a stable visual environment.

Patient J. R.

J. R. was seen for vision analysis 2 years post-TBI. He suffered a severe TBI in a motor vehicle accident. His chief complaint was double vision. He was referred by a local

optometrist for treatment of large constant exotropia. His case is notable because, although he had seen at least two ophthalmologists and an optometrist since his injury, no one had diagnosed him with a right hemianopia with visual neglect. He was unaware that he had a visual field defect. He and his family assumed that his spatial disorientation was simply part of his brain injury. When advised of the diagnosis, his mother asked if that was why he always veered to the left when driving. Fortunately, he had only been driving on their property. J. R. also suffered significant memory loss.

J. R. was seen on an outpatient basis, intermittently, for several years. Because he had no previous rehabilitation, working in a half day at the rehabilitation center several times a week and a vision therapy office visit once weekly proved to be a challenge for the family, and J. R. was inconsistent in his attendance and his homework. Nonetheless, over a period of approximately 18 months, the exotropia for which J. R. had been wearing a pirate patch for more than 2 years resolved with vision therapy. Therapeutic techniques included both orthoptic visual therapy and spatial organization. Scanning and visual memory therapy activities were prescribed and administered by occupational therapists and his parents. J. R. learned to scan effectively in familiar environments but had residual difficulty in busy, unfamiliar environments, such as the shopping mall. Unfortunately, although his memory improved, it remained significantly impaired.

Although his rehabilitation was extended due to less-than-ideal compliance, J. R. was happy to be rid of his patch and to have better ability to move about in his space. He continued to live with his parents and young son. Although he required cueing for many tasks, he was able to help raise his son, participate in sports, and maintain a part-time job as a dishwasher in a restaurant.

Patient C. L.

Patient C. L. was seen for visual evaluation 13 years after TBI sustained in a motor vehicle accident. Her chief complaints at the time of the vision examination were that her eyes rolled back in her head during seizures and she experienced some eyestrain although her occupational therapist had noted that C. L. complained of headaches and blurred vision after near work.

Examination revealed a convergence insufficiency exotropia (i.e., strabismus when viewing at near point due to inability to converge her eyes). She was diplopic almost constantly when doing tasks within arm's length. When queried about the diplopia, she said that the doctor she saw just after her accident had told her it would go away in time, so she just waited.

Although her phorias were not large (9 prism diopters of exophoria at near), she had almost no elicitable base-out reflex fusion and abnormal convergence ranges on prism vergence testing with a negative recovery (i.e., once fusion was broken with base-out prism, it required base-in prism to reestablish fusion). Her near point of convergence on push-up testing was 16 inches. Because she had so little fusion response, we were unable to prescribe any outpatient therapy.

C. L. was treated on a daily basis for 2 weeks, 45 minutes per day, using large fusion targets projected on a wall to attain peripheral fusion and SILO. Instrument (amblyoscope) convergence techniques were also applied. After 2 weeks, she was fusing well enough at near point that we were able to prescribe convergence exercises for practice with her occupational therapist at the rehabilitation facility. She continued in-office therapy once weekly and made continued progress with this regimen.

Patient L. R.

Patient L. R. was seen 4 months postinjury with chief complaints of poor depth perception and difficulty keeping things level. Examination revealed a mild (approximately 10 prism diopters) right esotropia and a mild left superior rectus palsy, which resulted in a noncomitant vertical component to the eye turn (6 prism diopters in primary gaze, increasing on left gaze). The superior rectus also intorts the eye. Her complaint of difficulty keeping things level probably resulted from a combination of extorsion of the eye and the noncomitancy of the vertical component. Pursuits were jerky. Ductions were full with the right eye and showed a superior temporal restriction with the left eye. Although she appeared to fixate with her left eye during the entire examination, she showed alternating suppression on her stereopsis testing. She also had reduced accommodative amplitude and facility.

Therapy progressed from monocular and biocular (i.e., two eyes open, without fusion) skills to antisuppression activities and in-instrument fusion with vertical and base-in vergences. After 12 weekly sessions in office with an hour of home therapy daily, her extraocular range of motion was full with each eye with smooth pursuits. She showed no vertical or horizontal phoria, at distance or near, and she was comfortable with her vision. Therapy was continued for six additional sessions to improve fusional and accommodative flexibility. At her 1-year progress check, she had maintained all of her visual gains.

Patient B. B.

Patient B.B. was seen for examination 4 months postinjury. He had no light perception from his right eye due to optic nerve atrophy following his injury. His left eye was healthy and intact. He presented with decreased acuity (20/80 when reading a vertical column and 20/30 when reading horizontally). He had reduced contrast sensitivity for medium spatial frequencies. He also had a left hemianopia with macular sparing. He had difficulty reading. He watched his feet when walking and tended to veer leftward. Saccades were slow and pursuits were jerky. He had a reduced amplitude of accommodation and was already wearing a bifocal correction, which he found useful. He read at approximately 8 inches from his eyes for the additional magnification.

B. B. was aware that he had a field defect but did little to compensate for it. The physical therapists had already taught him to use a walking stick on the blind side, both

for physical support and to protect that side. However, like most hemianopes, he did not scan toward the affected side. During tachistoscopic procedures, he generally missed the first few letters or digits, and he, initially, had poor perceptual speed and span. On line bisection tasks, he transected the line at the center or contralateral to the blind field. This is the expected performance for a patient with hemianopia combined with VSN rather than just a hemianopic defect. On some other tasks, his performance was consistent with a mild case of neglect. For instance, when instructed to scan a wall for target figures, he would scan from right (his intact field) to left. When asked to scan again from left to right, he would become argumentative, stating that he always scanned left to right and then would proceed to scan from right to left again. He showed few other indications of neglect. Copied forms were complete. On crossing-out tasks, he generally covered the entire page, always starting from right to left, but he was careful to reach the left margin of the page.

Therapy began with monocular skills and tachistoscopic procedures for perceptual speed and span. These skills improved rapidly with therapy. Peripheral awareness techniques for expanding awareness within his intact field were applied with good success. B. B.'s overall reading speed improved along with his saccadic speed, perceptual span, and perceptual speed.

A number of techniques were applied for making B. B. more aware of space within his blind field. Some of these met with more success than others. He rejected application of Fresnel prism, saying he would rather move his eyes farther without the prism. He actively participated in both tabletop and wall-projected scanning activities, trying to adopt an efficient scanning pattern, moving from far left in his blind field, rightward. However, initially, these activities did not seem to generalize outside of the therapy room. He was able to adopt a scanning pattern while walking. He looked left on every fourth step, which helped him walk without deviating leftward. His mobility and reading improved enough through his course of therapy that he was able to return to his life as a student at a junior college.

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APPENDIX 26-A

Organizations to contact for information regarding orthoptic or vision therapy or referral to member doctors who may provide or prescribe therapy:

Neuro-Optometric Rehabilitation Association, www.nora.cc, email: info@nora.cc

College of Optometrists in Vision Development, www.covd.org, 215 W. Garfield Rd., Ste. 200, Aurora, OH 44202, 330-995-0718

Optometric Extension Program Foundation, www.oepf.org, 2300 York Road, Ste. 113, Timonium, MD 21093, 410-561-3791

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Remediative approaches for cognitive disorders after TBI

MARK J. ASHLEY, ROSE LEAL, ZENOBIA MEHTA, JESSICA G. ASHLEY, AND MATTHEW J. ASHLEY

INTRODUCTION

Cognitive rehabilitation for people with acquired brain injury first became a clinical focus in the late 1970s. The sequelae of acquired brain injury were increasingly recognized as medical science became proficient at life-preserving practices following severe injury to the brain. Larger numbers of people survived traumatic and nontraumatic events alike that resulted in injury to the brain. Rehabilitation services were largely restricted to those rendered in an acute hospital setting, and available discharge settings consisted of the home, psychiatric hospitals, or skilled nursing facilities. The level of restitution of physical and communicative deficits achieved was insufficient to allow for a return of many of these individuals to independent and productive lifestyles.

The significant limitations of available settings were soon recognized by the private funding sector, which had a long-term financial responsibility for some of these people owing to the events surrounding their injuries. That is, workers' compensation and liability insurance carriers came to question whether further rehabilitative interventions might be developed to reduce the level of disability following discharge from acute rehabilitation hospitalization, thereby reducing the amount of assistance for physical and cognitive deficits that might be required and the lifetime costs ascribed thereto.

The field of postacute rehabilitation was born of this time and with it investigation into existing treatment interventions that had been developed for other neurologically impaired populations that might have applicability to persons with acquired brain injury. Physical disabilities were identified to be less disabling than cognitive disabilities, and this remains the case today. Cognitive disabilities continue to impose severe limitations on a person's ability to interact meaningfully and independently as well as in an age-appropriate fashion within most aspects of society. This is not to diminish the tremendous obstacles faced by people with physical disability but rather to point out that societal accommodation to physical disabilities has been greater to date, and accommodation to cognitive disabilities is both less prevalent and far more difficult to accomplish.

This chapter addresses cognition from a particular vantage point largely informed by psychological, psycholinguistic, and cognitive research. Cognitive skills and processes are discussed and rehabilitative avenues reviewed insofar as they are the focus of concern for persons with acquired brain injury. The information presented herein provides detailed insight into a particular approach to cognitive rehabilitation that has been used for over three decades and has been found to be effective in restoration of improved cognitive function following brain injury. Analogous approaches have been published and are not covered here.[1–3]

COGNITION

Cognition, in the simplest sense, refers to conscious mental activity, such as thinking, remembering, learning, or using language. However, cognition is a broad term that refers to mental processes that include, but are not limited to, perception, reasoning, judgment, intuition, memory, attention, problem solving, executive functioning, language, visual–spatial skills, awareness, comprehension, and psychomotor speed of processing.[4–6] Cognition includes the ability to mentally represent, organize, and manipulate the environment, a group of "*processes* by which sensory input is transformed, reduced, elaborated, stored, recovered, and used" (p. 4).[7] "Among these processes are attending (alertness, awareness, attention span, selective attention), recognizing, discriminating among stimuli and identifying similarities and differences, maintaining the temporal order of stimuli and responses to them, learning and remembering (including retention span and immediate, recent, and remote memory), organizing (including categorizing, associating, and/or synthesizing stimuli), comprehending, thinking, reasoning, and problem solving. Essential to the most efficient use of these processes is an adequately developed *knowledge base* (including general information, linguistic knowledge, academic skills, knowledge of social rules and roles, and much more). This knowledge base forms the basis of implicit knowledge or information. Cognition also includes the *use* of these processes to 1) make decisions as to the most appropriate and functional ways of interacting with the environment, 2) execute those decisions, 3) monitor responses to determine the appropriateness and accuracy of those decisions, and 4) adjust behavior if it is determined to be inappropriate and/or inaccurate" (p. S6).[4] A dimension of self-regulation of functional behavior is emphasized in the definition of cognition in order to promote a treatment focus on functional goals during cognitive interventions.[8]

Cognition entails specific skill sets (e.g., the ability to maintain a focus of attention) which, combined, form processes (learning, remembering, planning, problem solving). Interventions designed to improve overall cognitive function must, therefore, address both specific skill sets and processes. Because many cognitive skills combine to form processes of cognition, a review of the definitions here provides insight into the breadth and complexity of cognitive skills and processes. The American Congress of Rehabilitation Medicine[9] and the American Speech-Language-Hearing Association[8] guidelines combined may provide the most comprehensive inventory of cognitive skills and processes. These include attention, alertness, awareness, attention span, selective attention, stimuli recognition, stimuli discrimination, maintenance of the temporal order of stimuli, learning, retention, memory, organizing, categorizing, association, synthesis of information, comprehension, thinking, problem solving, decision making, planning, insight, reasoning, learning ability, maintenance of sequential goal-directed behavior with self-correction of responses, and emotionality.

Neuroscience tends to support the view of a highly interrelated and integrated system of cognitive function being subserved by the basic physiology. Amaral reviewed the neuroanatomical organization of information processing and stated, "A general principle of brain information processing is that it is carried out in a hierarchical fashion. Stimulus information is conveyed through a succession of subcortical and then cortical regions" (p. 388).[10] The various forms of memory represent some of the greatest cognitive processes supporting the ability to function independently and participate responsibly in social commerce. Tulving pointed to the componential and hierarchical nature of memory.[11] Tulving's concept of a hierarchical structure to memory systems included the idea that interventions that impacted a system at any particular level would necessarily impact the system as a whole. The hierarchical and interrelated nature of proposed memory systems, together with the underlying neuroanatomical and neurophysiological substrates, become important in determining an approach to designing interventions for memory system problems following traumatic brain injury (TBI).

Attention

Attention is foundational to cognition overall. It is the most basic of cognitive skill sets, and it impacts virtually all other cognitive skill sets. Posner proposed the organization of three attention networks: 1) a network for orienting to sensory stimuli, 2) a network for activating ideas from memory, and 3) a network for maintaining an alert state.[12] Attention consists of both orienting and executive attention networks. Arousal and alertness are basic components of orienting, and executive processes involve information processing of a potentially higher order and include selective and divided attention. Selective attention incorporates focused and divided attention for which filtering relevant from irrelevant information is required. Divided attention requires the division or sharing of resources between two or more kinds of information, sources, or mental operations.[13] Focused attention requires selection of one source of information while withholding response to irrelevant stimuli. Attention also has a construct along two dimensions: intensity and selectivity. Intensity involves the state of receptivity to stimulation, response preparedness (alertness), and attentional activation for specific target appearance within a stream of otherwise irrelevant stimuli (vigilance).[14]

The supervisory attention system (SAS) is hypothesized as the mechanism by which attention resources are directed consciously and subconsciously by the individual, thereby exerting some measure of cognitive control.[15] Attention can be controlled and uncontrolled. Through exercise of various measures of control, attention can facilitate enhanced awareness of a perceptual attribute, facilitate conflict monitoring and resolution, and facilitate response selection.

Sensory information entering the central nervous system (CNS) makes its way to the brain stem with the exception of visual and olfactory stimuli. Visual and olfactory

stimuli remain above the tentorium, and only oculomotor responses involve the brain stem. The reticular activating formation receives cortical, auditory, tactile, proprioceptive, and vestibular input. In addition, the reticular formation receives input from the cerebellum, basal ganglia, hypothalamus, and the reticulospinal pathway. The ascending projectional systems send information from the brain stem reticular formation to the nonspecific thalamic nuclei,[16] the hypothalamus, and the reticulospinal pathway. The ascending projectional system reaches the cortex via the widely distributed thalamic projections arising from the nonspecific nuclei. A broad spectrum of structures is involved in arousal and attention.

At the brain stem level, the mesencephalic reticular formation and its thalamic projections have been implicated in maintenance of arousal[17] and the orientation of attention.[18,19] In fact, substantial changes occur via the autonomic nervous system in relation to conscious direction of attention. These include changes in heart rate, vascular dilation, pupil size, and galvanic skin response.[20] The basal ganglia project to the cortex indirectly via the thalamus. Bares and Rektor studied the role of the basal ganglia in cognitive processing of sensory information and found the basal ganglia to be active in a contingent negative paradigm linked to a motor task.[21] Experience in Parkinson's disease has resulted in the suggestion that dopamine might play a role in regulating attention.[22] The striatum receives inputs from various cortical areas and projects principally to the prefrontal, premotor, and supplementary motor areas via the thalamus. These areas are involved in motor planning, shifting attentional sets, and in spatial working memory.[23] Nauta notes the circuitous connections between the cerebral cortex, limbic system, and corpus striatum in the overall fluidity of attentional processes.[24]

The thalamo-frontal gating system is implicated in selective or controlled attentional processes.[25] Distractibility may occur following disturbance of the diffuse thalamic projection system. Difficulties with interference and integrational behaviors of judgment, planning, and socially appropriate behavior are found with damage to the thalamo-frontal gating system. A fair amount of information processing occurs at the level of the thalamus. The purpose of the thalamo-frontal gating system is largely to direct selected information up to cortical structures. Incoming stimuli are enhanced or attenuated by the facilitation or inhibition of transmission of neural impulses there. Attention can, thus, be directed to specific stimuli while other stimuli are suppressed. Perception of stimuli at the cortical level only occurs when the diffuse projection system is also active.[26]

At the cortical level, frontal, posterior parietal, and cingulate cortices are involved in attentional processing.[25,27–29] The neocortex is involved in response selection based upon cognitive or semantic dimensions.[30] The associative cortices appear most active in attentional processes.[31] One hypothesis suggests that a competition for neural resources is created when cells in the associative cortex respond to a novel stimulus.[32] The number of cells available to respond to another stimulus is decreased proportionately to the number responding to the first stimulus. Experimental evidence supports this hypothesis in the finding that some pathways are facilitated by attention to a signal, and others are simultaneously inhibited.[33] Conscious processing of a stimulus causes a decrease in the ability to detect new stimuli.[34]

Information appears to be managed either reflexively or intentionally within the system. Schneider and Shiffrin refer to automatic and controlled processing.[35] Automatic processing is almost of unlimited capacity and rate. Controlled processing is serial and is limited in both rate and capacity. Anderson conceptualized these issues earlier as deliberate and automatic processing.[36] Tasks that require conscious direction of attention take up attentional resources, slowing or preventing information processing of other stimuli. Repeated task completion, however, may allow for deliberate attentional resource to be decreased, changing over to automatic processing and freeing system resources.[36]

It is easier to attend to different aspects of the same object than to attend to the same attributes in different objects. Some of these limitations are due to similarity of perceptual information of the attended information. Information presented in the same modality is harder to attend to than information coming from different modalities. Duncan demonstrated that ongoing cognitive processes, too, can interfere with the detection of new signals.[37] These include storage of recently presented information, generation of ideas from LTS, and development of schema.

Posner provided a description of the manner in which attention resources act upon events after biasing from the individual's mindset. He states, "Perhaps because of these limitations, much of perceptual input goes unattended while some aspects become the focus of attention. Attending, in this sense, is jointly determined by environmental events and current goals and concerns. When appropriately balanced, these two kinds of input will lead to the selection of information relevant to the achievement of goals and lends coherence to behavior. The system must, however, remain sufficiently flexible to allow goals and concerns to be reprioritized on the basis of changing environmental events. This balance appears to be adversely affected by major damage to the frontal lobes" (p. 620).[38]

Large amounts of information can be screened in the face of competing stimuli, such as in dichotic listening studies. Information retention appears to be based on specific features that are determined by the listener, and evidence suggests that selective attention occurs in the early levels of processing for both visual and auditory attention.[39,40]

The existence of a brief visual sensory register was demonstrated by Spurling.[41] Visual stimulus was first referred to as an *icon*, and the auditory equivalent of *iconic* memory is referred to as *echoic* memory.[7,42,43] Sensory registers, such as iconic and echoic store, allow for information to be entered without the subject paying attention to the source.[7] These sensory registers store information in a literal way, can be overwritten by further input in the same modality, are vulnerable to "wash-out," are modality specific, and have a

moderately large capacity. Similar mechanisms have been identified for olfactory and haptic stimuli.[44,45]

Although sensory registers can store a great deal of information, information is initially stored for very brief periods of time (less than 60 seconds) in iconic and echoic store mechanisms. Information that is retained beyond this time period is thought to have been processed and integrated into other memory structures or other cognitive processes. Note the similarity between these concepts and those of PTP, STP, and long-term potentiation (LTP). Rate of forgetting has been shown to be 1/4 to 2 seconds for sensory stores and under 30 seconds for STS. Rate of forgetting is very slow or does not occur in LTS.[46]

Sensory store mechanisms also have some limitations in capacity.[20,41] The size of sensory stores has been found to be dependent upon the nature of the information presented. Two different studies found that recall for words was between two and four words.[47,48] Crannell and Parrish found sensory store memory span to be between five and nine items, depending upon whether the items were digits, letters, or words.[49] In experiments in which words were strung together to form sentences, recall of up to 20 words was found.[49]

Deficits in attention are either related to the rate or capacity of controlled processing or dysfunction of higher level processes, such as the SAS. Divided attention deficits arise when controlled processing is limited and divided between two sources, resulting in overloading and relevant signals being missed.[50] Focused attention deficits occur when an automatic response interferes with the execution of a response produced by controlled processes.[50] Studies suggest that deficits in focused and divided attention occur largely due to speed of processing rather than interference by competing stimuli, inefficient sharing of resources, or switching of attention between tasks.[51] Longer reaction times in dual task loading suggest that selective attention impairments may be more evident when tasks load heavily on controlled processing or working memory.[51]

Perceptual features

The human perceptual system is inherently designed to give priority to certain types of perceptual cues.[52] Perception of certain cues is facilitated by basic physiological mechanisms. Others, however, are guided by experience. The visual system, for example, is physiologically predisposed to enable an individual to register the visual stimuli associated with a falling snowflake. However, only through experience could an individual gain an appreciation for different types of snow although all the perceptual information required to allow such discrimination is present to the less experienced observer. Sensory stimuli from different sensory systems will, likewise, have both physiological and experiential features. These features have been referred to as *perceptual attributes* or *features*. Some perceptual cues, particularly those arising from a physiological predisposition, have been found to be represented in different languages and cultures in so-called "natural categories."[53]

Perceptual features can be those that are descriptive of a physical characteristic (iconic) or those that are descriptive of functional characteristics (symbolic). The iconic features of a table may include that the table is made of wood, is 4 feet tall, is rectangular, weighs 200 pounds, is brown in color, and has a smooth surface. The symbolic features of the table may include that it is used as someplace to work or to eat. Perceptual features can also include "characteristics." For example, the characteristics of "pretty" or "fast" might be considered perceptual features of a car. Essentially, every noun, verb, preposition, adjective, and adverb can be a potential feature. Of course, perceptual features are not just limited to objects. Events also have perceptual features. A textbook chapter, for example, might have the perceptual feature of "boring" or "interesting." Every object or event is comprised of its perceptual features.[54,55]

The encoding of memory has been described as a process of utilization of perceptual features in the establishment of an internal representation of an event.[56] Perceptual features of an event, which can include the context of the event (external context), are combined with perceptual features that may arise from the individual's previous experience (internal context or implicit knowledge) to encode the event in memory. Each perceptual feature can also be used for recall of an event. Only those perceptual features that are utilized during encoding can be used for recall. "…The effectiveness of a retrieval cue depends on its compatibility with the item's initial encoding or, more generally, the extent to which the retrieval situation reinstates the learning context" (p. 678).[56] The memory trace, its coding characteristics, and persistence are by-products of perceptual processing.[57] Craik and Lockhart suggest that trace persistence is a function of the depth of analysis and that deeper levels of analysis lead to stronger, longer-lasting, and more elaborate memory trace persistence.[56] As sensory stimuli are converted to mental representation in the form of memory, the actual input attributes may be purged.

The perceptual features that are encoded at the time of stimulus presentation will impact both long-term retention and recall. Additionally, the integrity and nature of the organizational structure used or developed at the time of acquisition will impact long-term retention.[58,59] Long-term retention of information may be directly related to the depth of information processing of the sensory experience. "Highly familiar, meaningful stimuli are compatible, by definition, with existing cognitive structures. Such stimuli (for example, pictures and sentences) will be processed to a deep level more rapidly than less meaningful stimuli and will be well retained. Retention is a function of depth, and various factors, such as the amount of attention devoted to a stimulus, its compatibility with the analyzing structures, and the processing time available, will determine the depth to which it is processed" (p. 676).[56] Craik and Lockhart proposed a *level of processing* framework designed to account for how information progresses from STS to LTS.[56]

The level of processing framework theorizes that information transfer from STS to LTS is impacted by the degree to which the stimulus is processed. Superficial processing results in lesser likelihood of transfer of information to LTS, and more in-depth processing is more likely to result in such a transfer.

Craik and Lockhart proposed that attributes of encountered perceptual stimuli combine with the needs of the individual to determine both what information is recognized and to what degree it is stored.[56] Much of the totality of sensory experience is lost in the earliest stages of information processing when deemed not to be immediately relevant or "washed out" or overwritten in the early sensory store mechanism.[7] Information that is more familiar is processed more quickly and at a deeper level. Due to the individual's previous experiential encoding, a great deal more information becomes available compared to that available for relatively novel stimuli.

A perceptual assay is conducted beginning with the sensory registers. An overwhelming amount of information is available at any point in time to the system because both relevant and irrelevant information is being experienced. Stimuli with which the individual has experience will be recognized and processed more completely than novel stimuli unless the situation demands greater attention to the novel stimuli. The ability to discern perceptual features is physiologically quite keen. In studies in which a novel stimulus is presented and habituation is allowed, a slight change in the perceptual characteristics of the stimulus following habituation results in changes in the autonomic nervous system and EEG recordings.[60]

Perceptual salience has been described by many authors.[61,62] Perceptual salience results when a particular perceptual feature becomes the focus of inordinate attention, sometimes to the exclusion of recognition of other features. Perceptual salience can be so strong that it interferes with other cognitive processing. Developmentally, perceptual salience appears to assist in concept acquisition. Preschool-age children are more perceptually salient for variability than older children. Older children show no differential sensitivity between variability and constancy.[63] In fact, perceptual salience for variability lead 6-year-olds to make more overdiscrimination errors due to attention paid to feature differences that were irrelevant.[64] Reflectivity has been noted to increase while impulsivity decreased with age.[65,66]

The degree to which an individual can move freely among perceptual attributes will impact that individual's creativity and problem solving. Frequently, problem solving requires a novel use of perceptual features. The chair's iconic features of construction and height can allow the chair to be used as a ladder. However, perhaps the most salient feature of a chair is the symbolic attribute (function) of "to sit on." In order to problem solve the use of a chair in place of a ladder, the individual must be able to survey the chair's iconic features, ignoring its typical symbolic feature (function), and determine if the chair can safely be used to stand on. A chair on rollers might be deemed too unstable. Once this is accomplished, the novel functional application as a ladder may become stored as simply another acceptable functional application of the chair, thereby becoming a part of the individual's implicit knowledge about "chair."

Some perseverative behaviors following TBI may, in fact, be a manifestation of perceptual salience and a form of cognitive interference. Deficits in processing featural information have been noted in people with TBI[67] with observed patterns of response showing a tendency to base decisions upon a single salient feature and lesser likelihood of responding to complex multidimensional stimuli.

Categorization

Classification or categorization allows for large amounts of information to be managed.[68] Categorization is thought to be crucial to nearly all cognitive ability.[69] "In dealing with the world, people have a system for classifying objects into categories. The system makes these classifications on the basis of salient attributes like shape, size, function, and activity. …The systems for classifying and for naming are not really distinct" (p. 468).[70] Of course, categorical organization need not be restricted to objects but can include experiences. "Categorization may be what makes possible human perception, memory, communication, and thought as we know it" (p. 1013).[71]

The ability to perceive, assay, and utilize perceptual features is crucial to categorization.[72] Perceptual features become categorical descriptors and, as has been discussed, are critical for memory encoding and retrieval. In early developmental stages, perceptual salience for variability may support the individual's ability to encounter a broad spectrum of perceptual features. As experience with the environment increases and age advances, a tendency toward constancy emerges.[61] Experience with the environment allows efficiency in perception. That is to say, a novel experience with a chair requires maximal attentional and perceptual resources. As experience with the chair increases, the features of "chairness" become encoded, and future encounters with a chair place less demand on perceptual and attentional systems. Just as the specific perceptual features of a chair are grouped to both define the chair and encode it, large amounts of information from the environment must be dealt with similarly. Rosch developed a paradigm depicting three levels of categorization: basic, superordinate, and subordinate.[73,74] Examples of each would be vehicles (superordinate), cars (basic), and dragsters (subordinate). One's experience with a category and level of expertise determines the level of categorization at which one interacts and the amount of detail one is able to discern in observing exemplars of any given category. This concept fits well with that proposed by Craik and Lockhart.[56] These authors describe levels of processing that provide an explanation for the effects and efficiencies arising from prior experience during information processing.

Three styles of categorization have been found to be involved in information processing: *rule application*, *exemplar*

similarity, and *prototype similarity*. Each categorical process involves distinct regions of the brain. Exemplar similarity categorization involves the medial temporal and diencephalic structures and requires explicit memory. Exemplar-based categorization probably involves reference to memory storage areas of the cortex that correspond to the nature of the information being referenced, e.g., verbal recognition to the temporal regions. Experiments in which category naming is involved show routine activation of the angular gyrus in the left hemisphere.[75] When the stimulus used is presented pictorially, activation is seen in the occipital cortex, not the angular gyrus.[76]

Frontal lobe damage has been noted to impact rule application but not exemplar similarity. Specifically, the dorsolateral prefrontal cortex has been implicated in rule-following as seen via the Wisconsin Card Sort,[77] which requires discerning rules from observation and context relation. D'Esposito et al. showed the dorsolateral prefrontal cortex to be involved in rule-based categorization when the task required switching attention between mental processes.[78] For rule application, the individual must 1) "selectively attend to each critical attribute…," 2) "for each attended attribute, determine whether the perceptual information instantiates the value specified in the rule," and 3) "amalgamate the outcomes of Stage 2 so as to determine final categorization. The first stage involves selective attention, the second involves the perceptual instantiation of abstract conditions, and the third requires the working-memory operations of storing and combining information" (p. 1017).[79]

Prototype similarity categorization appears to call upon implicit representation. As such, use of prototype similarity categorization may be dependent upon the level of processing required to make categorical judgments based on available perceptual information or the lack of success in application of exemplar similarity-based strategies.

Utilization of perceptual features in categorization is referred to as the *featural approach* of categorization.[53,54,80–84] As a category is defined or created, category members vary in the degree to which they represent the category. In the category "birds," a robin is a fairly typical member of the category. Conversely, an emu is a member; however, it is not a typical member. "Typicality" is quite important in categorization. Members of a category share many, although not all, perceptual features. A core group of perceptual features is required of all category members; however, other frequently shared perceptual features may only be "characteristic" of the category and not required for category inclusion.

Typicality bears on processing speed.[53,85] Defining features are those features that are necessary of an item to be included in a category. Characteristic features are those features that are commonly seen but need not be present for category inclusion.[86] The combination of defining and characteristic features, or lack thereof, impacts verification time for category inclusion or exclusion.[84]

Processing speed, as measured through reaction time studies, is dependent upon access to categorical information and differences in categorical complexity.[84] It has been suggested that naming is actually an act of categorization and that word-finding problems in aphasic individuals might be viewed as concept formation disturbances.[87] Speed of problem solving appears to be assisted by object labeling.[88]

Development of categorization skills follows an acquisition sequence: 1) piling, 2) keychaining, 3) iconic categorization, and 4) symbolic categorization.[89] Piling occurs when the individual places all items in a single group without regard for shared attributes. Keychaining (or edge matching[89]) involves a serial ordering of members of the category with which only a single feature is shared between adjacent members. Items 1 and 2 might share color while Items 2 and 3 share shape. Items 1 and 3 may not share any attributes. Difficulties with keychaining are often manifest in the communication patterns of people with TBI. Discourse analysis shows that people with TBI have impairment of productivity, content, and cohesion.[90] A conversational topic is, in fact, a category. Language, on the other hand, is quite abstract and, consequently, tangential speech, or difficulties in maintaining topic cohesion, is most likely a manifestation of difficulty maintaining categorical boundaries.

In iconic categorization, iconic features or physical attributes are utilized for defining category members. Items are grouped on the basis of a shared iconic feature or features. Symbolic categorization requires that members of the category share a common symbolic feature or function.

Categories can be simple or rather complex, but categorization remains a binary process. The category "car" is fairly simple in that an item is either a car or not. The category can be complicated by adding adjectives and adverbs, such as "foreign" car or "fast foreign" car; however, the process remains a binary one.

Individuals with left hemisphere lesions experience problems in categorizing fruit and vegetable items but are able to categorize on the basis of perceptual features alone. Right hemisphere lesions, however, produce a reverse effect. Lesions in the left posterior hemisphere cause individuals to have difficulty with weak categorical boundaries that can lead to reclassification, and those with left anterior hemisphere lesions evidence highly categorical responses and categorical boundary rigidity.[91] These findings are consistent with a loss of cognitive flexibility observed with injury to the prefrontal cortex (PFC). Individuals with left posterior disease experience difficulty sorting words or pictures of objects into categories.[92,93]

Fluent aphasics have been found to have difficulty in the use of perceptual or contextual information and recognition naming.[94] People with Broca's aphasia and normals had no difficulty. In general, Broca's aphasics and individuals with right hemisphere lesions are more competent in categorization than fluent aphasics although categorization ability may not be normal.[95–97] Several studies have demonstrated that fluent aphasics have more or less difficulty with determination of category membership depending upon the "representativeness" or typicality of the stimulus.[95,98,99] A study evaluating the ability to verify category membership

and generate exemplars involving both fluent and nonfluent aphasics found that both groups required extended verification time and had difficulty in generating atypical categorical exemplars.[100] Ability to generate typical category exemplars was better for both groups. The study concluded that subjects experienced diminished representations of boundaries around the category's referential field.

Verbal recall of categorized and uncategorized word lists was evaluated in epileptic individuals with left or right temporal lobectomies and normals. The left temporal group had poorer performance in recognition and recall compared to normals. There was no difference between normals and the right temporal group for recognition or recall. Performance was enhanced for both groups with word lists that were categorized.[101] Verbal learning in amnesiacs and individuals with frontal lobe damage was studied using "categorizable" word lists. Individuals with frontal lobe damage did not spontaneously categorize the word lists whereas amnesiacs did. When categorization was forced, those with frontal lobe damage showed improved performance.[102]

Categorization and its many manifestations cannot be ascribed to a single area of the brain. In fact, some of the most exciting work has been done utilizing PET scans, functional magnetic resonance imaging (fMRI), and EEG. Naming actions and spatial relations have been shown to activate the left frontal inferior gyrus (frontal operculum), the left parietal lobe, and sectors of the left inferotemporal cortices.[103] Processing of familiar words involves the right prefrontal cortex, posterior left parahippocampal gyrus, left medial parietal cortex, and the right superior temporal gyrus, and novel words activated the left hippocampal region.[104] There appears to be an anterior–posterior functional differentiation involving the medial temporal lobe (MTL). The anterior MTL is crucial for processing of novel episodic information, and the posterior MTL is involved in processing for familiar verbal information.[104] Visual confrontation naming shows activation of the left frontal, bilateral temporo-occipital junctions, and inferior temporal regions with differential activation of the right inferior temporal cortex seen for living versus nonliving category items.[105] These few studies show how highly differentiated but distributed cortical structures are for categorical processes.

Cognitive distance

Piaget noted that, as an individual becomes better able to represent experience cognitively, he is better able to do so while being physically removed from the experience itself.[106] Availability and accuracy of information about an object or experience varies with proximity to the object or experience. For example, available information about a "table" is greatest when the table is present. Information availability decreases as proximity to the object decreases. A color photograph of the same object provides less opportunity for direct sensory appreciation of attributes than does the actual object. Likewise, lesser information is available in a black-and-white photograph, progressing to a line drawing, to the written word "table," to the spoken word "table," and finally, to the concept of "table." As feature availability decreases to sensory mechanisms, reliance upon previously stored information increases. Such reliance is logically dependent upon the extent of previously stored information as well as the structural integrity of the underlying neural network allowing either direct or indirect access to stored information. The neural network must allow access to distributed information stored in various cortical regions (e.g., category naming in the left angular gyrus, pictorial information in the occipital cortices).

Information is input to as many sensory stores as the individual needs to recruit to "experience" the table. Visual sensory stores take in lines, angles, and color and may allow for estimation of dimensions of the table and recognition of the material from which it is constructed. If visual sensory input is inadequate to determine information of interest, other sensory mechanisms, such as touch and audition, can be recruited to identify additional attributes or the individual may call upon experience-based stored knowledge to fill in missing attributes.

Because sensory information is first processed at primary sensory cortices, any amalgamation of multisensory information requires that information processing continue from primary sensory cortices to unimodal sensory cortices and on to higher-order sensory (associational) cortices. Of course, in instances in which the individual can rely upon exemplar or prototypic knowledge derived from previous experience with the object or event, information processing is impacted, usually more efficiently, although not necessarily. "The semantic representation of an object is composed of stored information about the features and attributes defining that object, including its typical form, color, and motion, and the motor movements associated with its use. Evidence from functional brain imaging studies of normal individuals indicates that this information is represented in the brain as a distributed network of discrete cortical regions. Within these networks, the features that define an object are stored close to the primary sensory and motor areas that were active when information about that object was acquired" (p. 962).[107]

The organization of the PFC for perceptual and executive function appears to follow a somewhat hierarchical neuroanatomical and neuropsychological ordering that enables progression from basic motor or sensory functions through higher order processes of increasing complexity, culminating in the highest order executive, perceptual, motor, linguistic, and cognitive function. Unlayering of the PFC through injury to structures within the PFC essentially impacts the higher order functions although lesser order functions may also be impacted or may remain intact.[108]

Figure 27.1 demonstrates both the organization of primary, secondary, and tertiary cortices in the depiction of the brain and the imposition of lower and increasingly higher order skills.[6,108] The skills are segregated into pre- and post-Rolandic (central) fissure locations and functions.

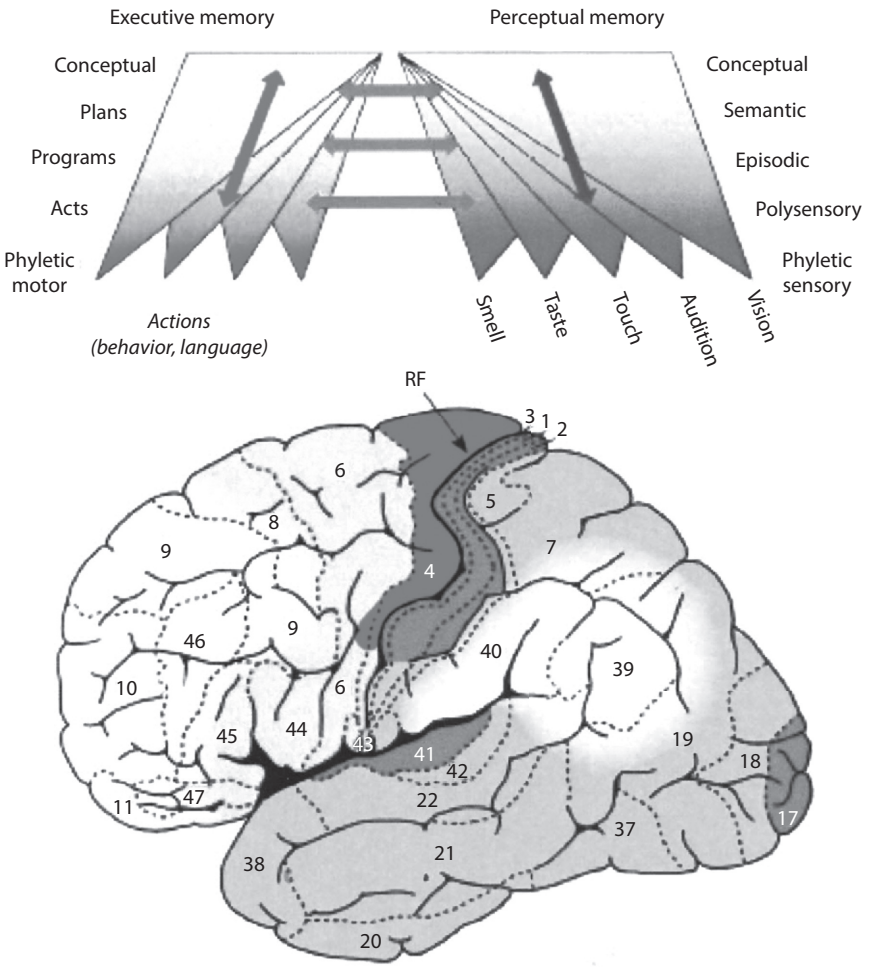

Figure 27.1 **(See color insert.)** General organization of cognitive representation in the human lateral cortex. **(Top)** Schema of the two major hierarchies of cortical memory. **(Bottom)** Distribution of memory networks indicated in broad outline by the same color code as in the upper figure. RF = Rolandic fissure. (From Fuster, J. M., The prefrontal cortex—An update: Time is of the essence, *Neuron*, 30, 2, 319–333, 2001. Reprinted with permission of Cell Press.)

Sensory functions are represented in blue, and "executable" or "actionable" functions are depicted in red. This diagram helps to provide a visual representation of the concept of cognitive distance progressing from bottom to top for both perceptual and executive memory functions.

Cognitive distance should be viewed as an important clinical entity for reestablishing the individual's ability to not only take in sensory information when it is readily available, but also to call upon information when available sensory information is reduced or, perhaps, absent. Burger and Muma showed that cognitive distance was a factor in aphasic and elderly nonaphasic individuals with whom performance was enhanced with objects contrasted to performance with pictorials of the same objects.[109] Muma noted similar discrepancies in performance with learning-disabled, developmentally disabled, and autistic children.[110] Muma reported improved performance by an autistic child when play with items in a real house with a real kitchen was compared to play with items in a toy house. The ability to abstractly identify features of objects or experiences that may be relevant to a situation depends upon both the ability to call upon stored featural information and the ability to use that information in both conventional and novel ways.

ASSESSMENT TOOLS

Individuals who have sustained TBI exhibit cognitive disorders in the areas of memory (long and short term), attention, processing speed, fluid reasoning, categorization, and shifting. Various formal measures have been utilized to determine the presence and extent of cognitive dysfunction, such as the Woodcock Johnson–III (Tests of Cognitive Abilities),[111] portions of the Scales for Cognitive Abilities for Traumatic Brain Injury,[112] Muma Assessment Program,[113] and the Ross Information Processing Assessment,[114] to name just a few. Due to the nature of the brain injury, modifications to formal measures may be required if the assessment is to be a true measurement of the individual's cognitive skills. For example, time limits are often a part of the diagnostic tool. However, if the individual is processing

information at a much slower rate, then it would be appropriate to allow for more processing time to complete tasks. Additionally, test items may be enlarged or simplified to accommodate for visual or motor deficits. Any modifications should be reported in the initial evaluation report. Extensive neuropsychological test batteries exist or can be compiled to carefully delineate a host of cognitive skills. The tests mentioned herein reflect those that can provide an efficient assessment and depiction of an individual's abilities relative to the skills discussed herein.

CONDITIONS FOR COGNITIVE REHABILITATION

A number of factors should be considered in determining whether the individual is able to benefit from cognitive rehabilitation. First, the CNS must be metabolically optimized to properly support rehabilitation efforts and learning. At the earliest stages after brain injury, metabolic function can be compromised by medications, cerebral edema, glucose metabolism anomalies, neuromodulator, neuroendocrine, and other biochemical imbalances. These factors, combined with other comorbidities commonly seen following TBI,[115] raise questions about the influence of these systems on a recovering CNS. Pulmonary, infectious, renal, hepatic, nutritional, or endocrine dysfunctions can all compromise cerebral function. General anesthesia and pharmacological iatrogenic complications can delay recovery following TBI. Consequently, the overall medical stability of the individual should be considered. Metabolic function is an ongoing concern beyond the immediate days or weeks postinjury.

At the metabolic level, neuronal death within the CNS can be accompanied by the death of adjacent and distant cells in the form of anterograde and retrograde axonal degeneration and deafferentation. Clearly, metabolic status impacts the extent of degenerative processes.[116] In some instances, cells in the vicinity of those that have died will enter a state of metabolic paralysis. These cells are only able to generate an action potential that is approximately one seventh the strength of a normal action potential. If metabolic compromise occurs while a cell is in a state of metabolic paralysis, these cells will likely succumb even to metabolic events that would not harm normally functioning cells.

Widespread/diffuse axonal injury (TAI) is a component of nearly all TBI,[117] and TAI impacts neurons, axons, dendrites, glial structures, and vascular supply.[118] As these authors point out, TAI represents a progressive condition arising from activation of cysteine proteases, caspaces, and calpains, which play roles in proteolytic digestion of brain spectrin following TBI. Additionally, overloading of calpains results in mitochondrial injury,[119] and mitochondria play a significant role in cellular necrosis and apoptosis. The end point of the progression of TAI is not yet clear.

Cellular death is also, in part, dependent upon the proximity of a sheared axon or dendrite to the cell body. Recovery from axonal shearing occurs via axonal sprouting and collateral sprouting although the latter is not dependent upon neuronal damage for elicitation.[120] Cortical representation is continuously modulated in response to activity, behavior, and skill acquisition in normal function. Environmental enrichment is known to bear positively on the density of dendritic, glial, and vascular structures.[121,122] Evidence suggests that similar processes occur following injury, either with adjacent areas taking over function or via use of alternative pathways.[123] Neuroanatomical changes that take place over long periods of time are represented by LTP, axonal regeneration and sprouting, and synaptic remodeling, at least. Rehabilitative therapy should represent such enrichment/demand paradigms. Appropriately designed programs have been shown by fMRI to impact cortical reorganization.[124,125]

Neuroendocrine function as a precursor to cognitive function, in general, is increasingly being recognized to be important. Neuroendocrine dysfunction arising from hypopituitarism following TBI has been found in up to 40% of persons tested.[126,127] Anterior pituitary function has been linked to cognitive outcome from TBI.[128] Growth hormone, sex hormones, leutinizing and follicle stimulating hormones, prolactin, thyroid, and cortisol function must be evaluated and treated prior to or during the undertaking of cognitive rehabilitation. This complex subject is addressed in this text in other chapters.

Fatigue and depression can complicate cognitive function. Cognitive dysfunction arising from these complications is significantly different from that arising from brain injury. It is important to identify these issues when they occur. Appropriate treatment of an underlying problem causing fatigue, such as neuroendocrine dysfunction or sleep disorder, will not only improve fatigue but also alleviate cognitive dysfunction arising from fatigue. Similarly, the cognitive dysfunction associated with depression should mitigate as depression improves. Treatment of cognitive dysfunction arising from fatigue or depression using the techniques to be described herein cannot be reasonably expected to be successful.

Timing of rehabilitation intervention must be considered as it may impact the efficacy of treatment because some interventions do not appear to be effective if undertaken too early after injury.[127] Interventions that are taken on early in the course of recovery may be difficult to differentiate from the effects of spontaneous recovery, and it becomes important to clinicians to utilize procedures that will enable such assessment, whenever possible.

THERAPEUTIC INTERVENTION

Cognitive retraining falls under two primary categories: remediative and compensatory. Remediative rehabilitation suggests that neuronal growth and synaptogenesis result directly from repeated exposure and repetition of stimulation through experience.[129] The compensatory rehabilitation model assumes that certain functions cannot be restored completely.[4] Therefore, strategies are used to

improve functional performance. Cicerone et al. reviewed the literature from 1998 to 2002 to establish evidence-based recommendations for cognitive rehabilitation.[130] Of the final 87 articles used in the review, the studies demonstrated effective rehabilitation of attention, memory, and executive functioning deficits through the use of different interventions. Strategy training was emphasized as a general principle. The utilization of a combination of remediative and compensatory rehabilitation approaches may offer an effective approach to cognitive rehabilitation. A subsequent evidence-based review by Cicero et al., including a total of 114 articles from 2003 to 2008, concluded that there was substantial evidence to support the use of interventions for attention, memory, social communications skills, and comprehensive neuropsychological rehabilitation.[131]

The interventions that follow have been designed to be approached in a hierarchical order that is fashioned after the normal developmental sequences observed in linguistic and cognitive development. Five primary areas of cognition will be considered: attention, memory, perceptual feature processing, categorization, and cognitive distance. As previously noted, attention, although often presumed to be the most basic of skills, clearly impacts and underlies most, if not all, aspects of cognitive function. The ability to identify and interpret perceptual features effectively is instrumental, in turn, to building categorization skills. Cognitive distance skills are accumulated and honed throughout the process of categorization. The assumption is that this collection of skills is foundational to most, if not all, other cognitive processes.

Given the interrelated nature of cognitive processing, it is important to conduct treatment in an organized and hierarchical fashion. All aspects of the treatment protocol to be outlined must be fulfilled in the proposed order and without omissions. Individuals who possess competencies in certain areas will progress through those modules very quickly but will nevertheless benefit from the developmentally oriented approach. Pre- and posttreatment testing using broad measures of neuropsychological function should be undertaken to document changes. Care should be taken in choosing test instruments to ensure that these tests do not measure specific skill sets being trained; instead, broader, more generalized measures should be used.

There are various ways to systematically alter therapeutic activities while regarding the three primary principles of environmental stimulus, task complexity, and cognitive distance. Table 27.1 shows the order of therapeutic task presentation, including variables, such as level of task and environmental complexities. Treatment should begin with performing physical tasks in a controlled and enclosed environment and ultimately progress to mental tasks in a stimulus-rich environment.

The environment must be modified to implement a step-wise progression through this hierarchy of attention. Therapy should initially be performed in a controlled and enclosed environment in which auditory and visual stimuli are minimal. The treatment area should be designed such that furnishings, therapy materials, lighting, and temperature can be managed. For example, an individual exhibiting a severe attentional deficit may require an environment with little visual and auditory stimuli present, such as a room without furniture, with low lighting, and temperature adjusted to their liking. It may be necessary for the therapist to adjust his or her attire to decrease color stimuli from clothing, remove jewelry, etc.

Once the individual can perform simple therapeutic tasks in the controlled environment, auditory and/or visual stimuli may be gradually introduced, moving from least to most salient and advancing in one sensory modality at a time. For example, therapy for an individual who enjoys rap or soul music may start with soft, relaxing music and then progress to more energetic music at louder levels, ending with the type of music the individual enjoys most and knows well. Similarly, initiating tasks in a sterile environment, one without furniture and other visual distractions, may be necessary. When the individual is able to perform tasks in simplified settings, visual stimuli can gradually be introduced. It may be necessary for all disciplines to conduct their therapies in a sensory-controlled environment to achieve maximum therapeutic benefit.

An important part of the therapeutic process involves task complexing. In consistency with the framework of a bottom-up approach, tasks should start with physical activities and gradually progress to mental activities, utilizing a taxonomy of cognitive distance. Physical activities can include sorting/categorizing by iconic features, such as color or size, whereas abstract activities might include symbolic categorization. Complexity is increased by adding more objects or lengthening the time required for engaging in tasks. For example, the individual may be required to attend to tasks for 10 seconds. Once this is achieved, the individual should be required to perform this task consistently with 80% accuracy. The next level would involve increasing the length of time engaged in the activity. When working with severely impaired individuals, it is often necessary to perform a single therapeutic activity repeatedly for lengthy periods of time to build basic attention skills. It is important to monitor accuracy and response time to

Table 27.1 Order of distractor presentation

	No distractor	Simple auditory or visual distractor	Multisensory distractor
Physical task	1	2	3
Physical/mental task	4	5	6
Mental task	7	8	9

determine when it is appropriate to move the individual to the next level of difficulty.

The therapeutic environment should continually challenge the individual until, ultimately, activities are performed with satisfactory accuracy and sustained attention in a stimulus-rich environment. It is imperative to ensure that data is collected throughout the therapeutic process, including changes in environmental complexity. A general criterion for increasing task and environmental complexities for physical activities is 90% to 100% accuracy whereas 80% accuracy is appropriate for mental activities. Time limits to perform tasks can be modified depending on the individual's physical limitations. For example, when analyzing the task completion time, the therapist should note whether processing speed was impacted by the existence of a physical impairment, such as the use of a nondominant hand.

The principles of cognitive distance previously mentioned in this chapter must be taken into account. Treatment should begin with the utilization of objects because objects are most concrete. With an object, individuals have the ability to physically determine size, weight, color, texture, etc. As cognitive distance increases, use of pictorials (color, black and white, and line drawing photographs) is introduced.

Attention

One of the major cognitive deficits following TBI is impaired attention. This can include complaints of inability to concentrate, sensitivity to perceptual noise, alternating between tasks, or difficulty with task completion or multitasking. Although therapists often recognize the manifestation of attentional deficits, the underlying cause may be difficult to precisely identify. For example, when an individual presents with "distractibility," the therapist acknowledges the need to simplify the environment; however, this does not adequately address the complex nature of the attentional disorder, nor does it afford any form of remedy for the underlying cause. Intervention techniques targeting only one aspect of the disorder will not result in true and consistent improvements of the disorder as a whole. What is instead required is a technique that addresses the impairment in attention itself rather than merely its manifestations. Additionally, the same is true for individuals who display perseverative behaviors. The term *perseveration* does not adequately communicate the complex essence of the disorder.

A holistic approach to outlining the deficit is beneficial in the assessment and treatment process. Although there are several manners in which to address attention, designing a bottom-up therapeutic program allows for a developmental approach to building attention skills. Taking this approach with all individuals exhibiting attentional deficits ensures that all skills have been acquired in a developmental and sequential fashion, setting the foundation for higher-level cognitive processes.

At the base of the hierarchy lies *sustained attention*. This is the individual's ability to direct and maintain focus with regard to a task across a period of time in a quiet environment. Therapeutic activities addressing categorization, memory, visual and auditory processing, direction following, shifting, and problem solving can be performed to address the development of attentional skills. Physical or concrete tasks, such as sorting, scanning, and direction following, should be initiated first. Individuals with very poor attention may start with simple auditory sustained attention or vigilance tasks. Such tasks require the individual to listen to a string of stimuli targeting a specific number, letter, or word for short periods of time. Once attention and accuracy improve, the length of time may be extended. The same hierarchy can be utilized for visual sustained attention tasks. For example, the individual can sort picture cards or hardware pieces into different categories. Visual scanning or vigilance tasks can involve searching magazine articles for a target word. Again, once this task has been mastered, the addition of multiple targets further challenges attentional skills. Auditory scanning activities involve listening to stories or passages and indicating a targeted response for a designated word and then increasing the number of target words. Basic level strategies to improve accuracy on concrete tasks include teaching systematic scanning, double-checking work, and increasing awareness of attention deficits.

The next level in the attentional hierarchy is *selective attention*. Consistency must be established prior to moving the individual to a higher distractor level. Once the individual exhibits the ability to consistently perform tasks in a quiet and controlled environment, a hierarchy of distractors should be introduced. Initially, noise (e.g., a radio playing) should be presented in the controlled environment. Then, the individual can be moved from the controlled environment to a familiar environment with minimal distractors. This might simulate a person in a living or family room, providing the individual with the opportunity of a chance conversation and/or the presence of others nearby. To further challenge the attentional system, the next level should require the individual to perform tasks in a highly distractible, familiar setting (e.g., lobby, lounge, or gym areas). Finally, the individual should be placed in unfamiliar and high traffic areas (e.g., mall, bowling alley, bus station, etc.) to provide a maximal distractor-laden environment.

Once individuals demonstrate the ability to maintain attention in a distracting environment with good accuracy on concrete tasks, more mental or abstract tasks can be implemented. Working memory tasks, such as reordering a string of random numbers from smallest to largest or in reverse order, are more cognitively challenging. Several Attention Process Training[132] (APT) tasks involving attention, processing, and categorization may be initiated. These tasks involve listening to a string of words and identifying items that fit into a designated category (e.g., round objects, pairs, related words, opposite words, etc.). Other APT working memory tasks include listening to sentences and reorganizing the words within the sentences in alphabetical, reverse alphabetical, and/or progressive word length order.[132] Mental math calculations can also be performed.[132]

Higher level visual processing tasks, such as iconic store modules, may also be chosen. This task involves the individual viewing a card with three rows of letters for a brief period of time (2 seconds) and then being asked to recall a specified row. The generalization of quick visual processing can be facilitated through setting up a scene in a room and having the individual enter the room for a brief amount of time. Upon leaving the room, the individual would be required to recall as many details as possible.

Next in the hierarchy of attention is *alternating attention*, which refers to the ability to alternate attention from one activity to another with the least amount of interference to sensory stores, task sequencing, and task accuracy. This cognitive skill is hierarchically more complex and is often impaired in the individual with TBI. Basic level attention should be relatively intact prior to addressing cognitive shift skills.

Cognitive shift activities should adhere to the concepts of task complexity and presentation of external sensory stimuli. Activities should begin with two simple physical tasks, requiring the individual to shift from one activity to the other and back. Data collection includes response time to shift between tasks and accuracy of task completion. Once the individual demonstrates competency with physical tasks, task complexity should then progress to physical and mental, then to mental only. Tasks can be further complicated with the addition of external sensory stimuli. Table 27.1 can be referred to for the order of distractor presentation.

Physical tasks include simple rote motor tasks, such as linking chains together or sorting objects by a designated iconic feature (e.g., color, shape, size, weight, etc.). Mental tasks include sorting picture or word cards by categories, sorting objects by a designated symbolic feature (e.g., things that provide light, things that are used for scooping, things that make noise), performing various math calculations, etc. Recalling a sequence of shifts can be added for increased complexity. A telephone book scanning activity can be performed involving the individual locating addresses and phone numbers of businesses in a specified order. Other tasks addressing shifting can be located in the APT kit.[132] For example, one task may be to listen to a string of words and alternate between identifying fruits and articles of clothing throughout the task. Higher level shifting tasks address memory, initiation, and time management by incorporating visual and self-regulating tasks into the treatment program.[132] Now, the individual no longer has an auditory cue from the therapist but rather is presented with a visual cue and/or a specified time interval to shift. Two or three sets of instructions are told to the individual. Visual tasks require the individual to shift when presented with a visual signal. For example, when performing a visual scanning activity, visual marks should be placed randomly throughout the page. When the individual arrives at a visual mark, he or she must first recognize the mark to be a symbol, recall which set of instructions to perform, and then initiate the task to be performed. Self-regulating tasks require the individual to self-initiate alternating between two tasks at specified time intervals by monitoring time on a stopwatch. For example, when provided with math worksheets, addition tasks are performed initially. The individual performs the math calculations while simultaneously monitoring time. After the established time interval (e.g., every 30 seconds), the individual must then recall and initiate the next set of instructions. These tasks can also be performed with the hierarchy of distractors presented in Table 27.1.

The highest level of attention is *divided attention*, which requires the ability to attend to two or more different tasks simultaneously. Individuals divide their attention while driving, taking notes in class, performing household chores while watching television, etc. Divided attention can be addressed in a variety of ways, such as performing previously mentioned concrete and abstract tasks while simultaneously answering a series of questions differing in levels of complexity. For example, the individual may be required to sort hardware pieces into categories while simultaneously responding to yes/no or open-ended questions of varying complexity. The therapist can document response time to complete the sorting task, the percentage of correct responses, and any delay in responses to questions. In this way, processing speed can be monitored not only for task completion, but also for frequency of delayed responses.

Perseverative behaviors are another type of attentional deficit. A perseverative response may be characterized as an inability to shift a focus of attention among perceptual features. Therapeutic activities that decrease perceptual salience and establish the use of iconic and symbolic feature identification skills usually result in a reduction of perseverative responses. For example, the therapist may present an object to an individual and direct his or her attention to various perceptual features of the object such as color, shape, construction, etc. Some perseverative behaviors, however, may be a result of perceptual salience in other sensory domains, such as self-abuse as a result of sensory integration deficits. Treatment for improving perceptual salience will be discussed later in this chapter.

Attentional deficits also include problems with *vigilance*, referring to the ability to sustain a focus of attention and regulate perception of incoming information for a particular set of features. For an individual to be successful, he or she must first be able to quickly take in large amounts of visual and/or auditory information, resisting distractions of extraneous stimuli, and then be able to filter that information for the preferred feature(s). This process requires quick processing speed and increasingly abstract cognitive distance skills. Thus, therapy should address sustaining attention in a multisensory environment and building cognitive distance skills.

Throughout the progression of the attention hierarchy, impulse control should be in the forefront of the therapist's mind. Awareness of deficit and self-monitoring techniques should be explored and implemented. For example, prior to the initiation of a task, it would be appropriate to ask the individual to predict his or her success on the specific

task. Following the completion of the task, any errors made should be reviewed and correlated to the individual's prediction. Based upon the difference between predicted and actual performance, strategies for improving attention can be discussed.

Memory

Memory is a component of cognition that entails the ability to encode, store, retain, and recall information. In describing memory, the typical metaphor used is that of a filing cabinet or computer that can store many folders and files. However, memory is much more complex than a "filing system." There are a variety of types of memory. In the late 1960s, Richard Atkinson and Richard Shiffrin first described their model of memory as a sequence of three stages, from sensory memory to short-term/working memory to long-term memory as opposed to a single/unitary process.[46]

Sensory memory is the ability to retain impressions of sensory information after the original stimuli have ended. It acts as a kind of buffer for stimuli received through the five senses that are retained accurately but very briefly. For example, prior to the days of the Internet, one could dial the operator to find the phone number of a store. Once the operator stated the seven digits, that information was in memory until the last number in the phone number was dialed. Then, the phone number was washed from memory. Therapeutic tasks that address auditory or visual sensory memory include echoic store and iconic store tasks. The echoic store task utilizes cognitive processes, including attention, working memory, auditory recall and processing speed. In this task, numbers are presented verbally in a random order and the individual is required to organize the numbers from smallest to largest. This task begins with the presentation of three numbers and progresses to seven numbers, the length of a phone number. The goal is to achieve at least 80% accuracy over three consecutive trials for seven numbers in a quiet environment and then again in a distracting environment. A corresponding visual memory task is iconic store, which utilizes cognitive processes including attention, visual memory, and processing speed. In this task, a card containing three rows of three letters is presented for 2 seconds. The card is then removed and the individual is asked to recall a specified row. Two scores are recorded. The first score represents accuracy of the response of the specified row (with the goal being at least 70% accuracy), and the second score represents accuracy of the response for the entire card (with the goal being at least 90% accuracy). Once the goal is achieved in a quiet environment, the task is repeated again in a distracting environment with the same goal of 70%/90% accuracy for the line/card score, respectively.

Short-term or working memory is the ability to retain information in short-term memory and process that information simultaneously. Short-term memory acts as a kind of "scratch pad" for temporary recall of information that is being processed. Short-term memory has a limited capacity. Most individuals are able to hold approximately seven pieces of information in their short-term memory. "Chunking" refers to the ability to organize information or material into shorter meaningful groups to make them more manageable and can lead to an increase in the short-term memory capacity. For example, chunking a phone number into groups of three and four digits is easier than having to remember a string of seven numbers. Examples of working memory include addition or subtraction exercises that involve carrying or borrowing, language translation, and following a sequence of directions. Echoic store, mentioned above, is an example of an auditory working memory task, and iconic store is an example of a visual short-term memory task. Another example of a visual memory task is Memory Span, from the Parrot Software computer program.[133] Numbers are displayed on the screen for 3 to 5 seconds and then disappear. The individual is then expected to place those numbers in the same order as they appeared on the screen. The goal for this task is to achieve at least 80% accuracy. Response times vary depending on how many numbers are displayed on the screen. Typically, the target response time is 1 second above the numbers displayed. For example, if working on five numbers, the target response time would be 6 seconds.

Long-term memory refers to the ability to store information over a long period of time. Short-term memories can be converted to long-term through the process of consolidation, involving rehearsal and meaningful association. In the brain-injured population, memory for "old" information is typically most intact. Individuals usually do not forget who they are or major events that occurred in their life. It is the ability to learn *new* information and store or recall that information that is difficult for most individuals with brain injury.

Another type of memory that should be addressed is *prospective memory*, which refers to the ability to remember information or actions to be completed in the future or "remembering to remember." Assignments can be provided to an individual to complete at a date or time in the future. Strategies utilized to assist with recall of the information can include day planners as well as more sophisticated technology, such as cell phones or PDAs.

Feature identification

A therapeutic tool known as the *cognition module* can be used to improve overall cognitive functioning in a structured and developmental manner. At the first level of feature identification, the individual is trained to attend to and identify different perceptual features of real objects. Perceptual features can be broken down into seven iconic and one symbolic feature. Iconic features consist of, but are not limited to, color, shape, construction, size, weight, texture, and detail. The symbolic feature requires the individual to identify the function of objects. The list of perceptual features reflects some of the "linguistic universals" referred to by Rosch.[53]

Cognitive distance is introduced at Level I. The individual describes the iconic and symbolic features of real objects. Cognitive distance is built by moving the individual through a hierarchy of sublevels consisting of objects, color photographs of objects, black-and-white photographs of objects, line drawings of objects, written words, and ultimately, spoken words. When objects are no longer physically represented, the individual is required to rely on mental representation of objects.

Initially, a checklist of the eight perceptual features may be required. Once the individual begins to learn the features in an organized manner, the checklist can be phased out. Criterion for successful completion at this level is individually based. Although it is important to monitor accuracy at each sublevel, the therapist should keep in mind the broader scope of performance. Therefore, a comparison of the overall performance between sublevel objects and spoken words should determine whether the individual is ready to progress to the next level. For example, individuals may demonstrate difficulty at lower sublevels; however, through repetition, accuracy may improve at the spoken word sublevel. Because the individual has achieved greater task accuracy at a more cognitively distant task, it can be inferred that the individual's level of cognitive functioning has improved. Response times should be fairly quick; however, this should not be used as a criterion for progression to the next level as individuals with brain injury commonly present with slower processing speed.

Level II requires the individual to expand feature identification skills. The individual must still identify the eight features one by one and must also provide an extended feature. For example, when describing a stop sign, the individual must verbalize that the stop sign is red and must identify another object that is also red, such as an apple. Responses provided must be different for each of the eight extended features, thereby maximizing categorization, word finding, and memory skills. Additionally, the extended feature response should not be an object within the individual's visual field. The cognitive distance hierarchy ranging from real objects to spoken words should again be followed.

Level III focuses on abstract negation. The purpose of this section is to further expand feature identification skills through negative categorization. At this level, the individual is required to identify the eight perceptual features of the object in terms of what the object is not and then state another object that does not have the same characteristics. For example, when describing a stop sign, the individual must verbalize that the stop sign is not blue and must identify another object that is not blue, such as the sun. Again, the cognitive distance hierarchy ranging from real objects to spoken words should be followed.

It is often difficult for individuals with TBI to provide extended and negative feature identification secondary to decreased visual imagery skills. Visual imagery is important in everyday life to assist with episodic memory, abstract thinking, and problem solving. Often, individuals exhibit a limited repertoire of responses secondary to decreased visual imagery, word finding, and categorization skills. Several strategies can be used to assist with these skills. For example, visual imagery cues can assist with visualizing familiar places, such as different rooms in a house, playground, garage, mall, or office. If the individual is unable to verbalize an extended feature, further visual and/or semantic cues may be utilized. For example, if the individual was unable to visualize something in a kitchen that was also yellow, a cue to think of a fruit or something in a refrigerator may help trigger a response. With an increase in cognitive distance, for example, at the spoken word level, the inability to recall a target item is often observed. Cueing the individual to recall previous responses may be beneficial. However, providing structure to the task, such as having the individual state the name of the object prior to describing each feature, is usually more effective. Individuals with decreased word finding and visual imagery skills often repeat responses. In these cases, it is imperative that the therapist monitor responses and provide cues to generate novel responses as needed.

Mental flexibility is another skill that is addressed throughout the cognition module. The ability to perform negative categorization is significantly impacted by the individual's mental flexibility, visual imagery, and cognitive distance skills. When provided with an object (e.g., a banana), the individual with reduced mental flexibility will often say, "The color is not yellow." However, with cues, such as verbalizing colors other than yellow, and repetition of the task, mental flexibility is noted to improve.

Categorization

The next level of the cognition module requires the individual to identify iconic and symbolic features of objects grouped together. Each sublevel is divided into two steps. As suggested by the cognitive distance hierarchy, activities again begin with real objects, in this instance arranged in three rows with three objects in each row. The first step requires the individual to identify one perceptual feature in common across the three rows. For example, if rows of red, yellow, and blue objects are set on a table, the individual must recognize the common perceptual feature as being "color." The next step of this level requires the individual to identify three different perceptual features. Therefore, each row targets a different feature. For example, the first row can consist of items of similar "color," such as a fork, spoon, and knife. Another row can consist of items of similar "shape," such as a ball, plate, and tire. The last row can consist of items of similar "function," such as a flashlight, candle, and penlight. To further address mental flexibility, the therapist can ask the individual to provide additional responses. For example, in addition to color, a fork, spoon, and knife have the same shape, construction, size, texture, detail, and function. To promote effective problem solving and impulse control, the rows of objects can be manipulated such that the individual is required to scan the three rows prior to committing to a response. At this level, the cognitive distance hierarchy progresses to written words and

does not include spoken words. The strategy of process of elimination can also be taught to facilitate effective problem solving.

Level V of the cognition module requires symbolic categorization. For some individuals, symbolic categorization may be less difficult than iconic categorization. Research indicates that symbolic categorization may be more easily stored.[134] However, this may not be reflective of an intact feature processing system. Therefore, although it may appear that the individual has a basic understanding of symbolic features, this may only be a cursory understanding of common functional attributes of objects and not a true representation of proficiency in feature identification and categorization skills.

The purpose of this level is to develop the ability to categorize objects by function. This level consists of three steps and three levels of cognitive distance (color photographs of objects, black-and-white photographs of objects, and spoken word). If photographs are too abstract for an individual to begin with, it may be necessary to first use real objects. When shown a photograph of an object, the first two steps are to identify the traditional function of the object and the category to which it belongs. The next step involves verbalizing three alternate functions of the object. This includes functions the object can perform but that are not typically done with the object. For the last step, the individual must shift his or her perspective and identify three functions the object cannot be used to perform. At this level, the individual must integrate all iconic and symbolic features to think of alternative and negative functions of objects. For example, alternative functions of a fork may be to dig, stir, scratch, use as a hair clip, use to poke holes, or use as a screwdriver. To visualize these functions, analysis and synthesis of iconic and symbolic features must occur. Therefore, because the construction of the fork is strong and hard and it has a long, flat handle and sharp tines, it should be able to carry out the functions mentioned previously. For individuals who exhibit poor mental flexibility, it may be necessary to bring their attention to the eight features of the target object. The same cues may be used for identifying negative functions of objects. Additionally, having the individual recall the traditional function of the object and then determine other objects that do not serve the same purpose may assist with negative categorization. Again, therapists should closely monitor individuals' responses to discourage repetitive responses and facilitate a wide spectrum of responses instead.

Perceptual attribute prioritization is then performed to address more complex language and cognitive concepts while encouraging creativity. This task requires the individual to identify whether each of the perceptual features is important or not important to the function of the object and provide a rationale, for example, if the stimulus were a pen:

Color: Not important because it can be any color and still be able to write with.
Shape: Not important because it can be round, rectangular, etc., and still be able to write with.
Construction: Important because it cannot be made out of noodles or water, etc.
Size: Important because it cannot be ½ inch or 100 feet as you would not be able to pick it up and hold in your hand to write with it.
Weight: Important because it cannot be 1,000 pounds as you would not be able to pick it up and hold in your hand to write with it.
Texture: Important because it cannot be sharp as you would not be able to pick it up and hold in your hand to write with it.
Detail: Determine whether the object has a detail that if not present would preclude it from performing its function; A pen must have ink, otherwise, you would not be able to write with it.

A multisensory visualization task is next performed to further enhance cognitive abilities. The task requires the individual to describe a given experience using the five senses as well as generating emotionally based responses relevant to the situation. Initially, it may be necessary to target familiar experiences, such as a high school football game, a child's birthday party, Christmas Eve, or hobbies, etc. In the football game example, a response might include, "I see two teams in different uniforms, blue and white, red and gold, on the field. The chalked lines are clean and fresh. It's cold, and the wind is steady. I smell the hot cocoa and hot dog being eaten by a friend. The crowd is cheering, following the lead of the cheerleading squad. The bench is hard, cold, and uncomfortable with no back support. We use an old sleeping bag to spread over our legs for warmth. It's fun here with my friends, and I am excited that our team may win this championship game." As the individual's visual imagery skills improve, increasing the cognitive distance by having the individual describe situations or experiences he or she is not familiar with can be used. Previously learned skills, including feature identification, categorization, cognitive distance, perceptual salience, and visual imagery, are inherent to the successful completion of this task. As responses are subjective, the ability to express and support opinions can be concurrently addressed at this level, thus improving the expression of complex ideas.

Processing speed can be monitored by timing the individual's responses in the different levels of the cognition module. When progressing to higher levels or increasing the complexity of tasks, response times may become lengthier. However, it is expected that response times will improve with repetition. When comparing performance on a lower sublevel to a higher sublevel (objects, spoken word), if response times maintain, it can be inferred that processing speed actually improved secondary to the increased cognitive demands of the higher sublevel. Other tasks to help improve processing speed include performing word fluency activities, such as naming as many items within a concrete category (animals, modes of transportation, occupations, etc.) or an abstract category (naming words beginning with a specific letter of the alphabet).

The cognition module assists with the overall thought organization process in numerous ways. These include the ability to move freely among perceptual attributes; diminishing or eliminating perceptual fixation; improving registration of available perceptual information; improving feature availability for information encoding and subsequent retrieval; improving memory encoding and retrieval; improving problem solving; improving all levels of attention; and improving cognitive distance, processing speed, depth of processing, categorization, information management and processing efficiency. The initial task is to learn the iconic and symbolic features in an organized manner. Therefore, it is important to consistently cue the individual to a specific order allowing for improved organization and efficiency of information processing. Cognitive skills, such as attention, feature identification, categorization, cognitive shift, and cognitive distance, are required simultaneously. Interference from perceptual salience (an excessive amount of attention to a particular perceptual feature) can be restricted through the use of seven iconic features and one symbolic feature. Categorization skills are optimized throughout the module by initially performing feature identification tasks using iconic and symbolic features. Each level consists of sublevels that address cognitive distance, requiring the individual to rely heavily on mental representation of objects by diminishing the amount of physical information presented.

The therapeutic tools reviewed in this chapter are designed to reestablish basic level cognitive abilities. Higher level thought processes and memory cannot be adequately addressed if basic level cognitive skills are not first put into place. The cognition module is not meant to be the only treatment activity; rather, it is an essential part of the overall rehabilitation program.

Constantinidou et al. performed a scientific study to explore the effects of a systematic categorization program (CP) to determine the efficacy of categorization training in individuals with TBI during postacute rehabilitation.[3] Neuropsychological testing on cognitive function was assessed initially and again at discharge. Additionally, throughout the structured program, three probe tests are administered to determine how individuals generalize information learned on the CP to other tasks not directly related to the CP training tasks. The CP protocol incorporated portions of the cognition module into a structured, therapeutic tool. Although both the experimental and control groups demonstrated progress in neuropsychological performance after completion of the treatment program, the participants who received the CP protocol demonstrated greater gains.

NEUROANATOMY OF THE COGNITION MODULE

In this section of the chapter, we assign aspects of the cognitive interventions described to their respective neuroanatomical substrates when possible. To begin, each of us has encountered a situation in which we needed to adapt an object or process to a purpose for which it was not designed in order to accomplish a given objective. In fact, in many ways, this ability is one of many in which human cognition differs significantly from that of lesser species. In effect, this is the heart of innovation, the recognition of salient attributes of a useful object or process that would serve the necessary function to accomplish a goal.

Both simple and complex examples of such situations abound in everyday life. A common, simple example might be one that has frustrated most of us at some point or another: when an item falls into the crevice between the seat and the console in an automobile such that it cannot be reached by the driver but must nevertheless be retrieved. There exists a multitude of possible solutions to this simple problem in theory, but in practical application, only a handful of these might be available in a particular instance as the available tools within the vehicle are likely to be limited. So the solution to the problem becomes one that must be derived, if possible, from the available tools or processes at the time. One such solution would be to use a pen to extend the reach of the driver and push the object free; another might be to have a child, whose smaller hand or arm could extend more readily into the narrow gap, reach for the object; a third might be to use an object tailored to the attributes of the fallen item, such as a magnet, to retrieve keys or a piece of tape for a dollar bill; still another might be to reposition the seat forward or backward in order to more easily reach the object. We will return to this example in our examination of the cognition module as a therapeutic tool later.

First, it is worthwhile to point out that even the most complex problem solving relies on essentially the same elements as our simple one. Namely, determination of the characteristics of the problem, identification of the necessary features or attributes of a solution, identification of a solution to the problem, followed or preceded by comparison of those attributes in relation to a specific object, process, or combination thereof and subsequent application of the object(s) or process(es) as the solution to the problem. The modern concept of vaccination evolved via this process. In solving the problem of the smallpox epidemic, astute and observant scientists recognized that certain strains of the smallpox virus that did not result in severe disease had the attribute of conferring immunity to all other strains of the virus. These scientists recognized that this attribute could be used to prevent severe smallpox disease if the particular nonsevere (also referred to as nonvirulent) strains of the virus were administered systematically to healthy individuals. In effect, this formed the theoretical basis for attenuated live vaccinations and paved the way for all modern forms of vaccination.

Based upon the premise that the recognition of features or attributes of objects or processes and subsequent application of this to problems underlies most, if not all, forms of problem solving, a logical target for therapeutic intervention would be to induce or improve this type of identification and categorization. In essence, the cognition module is

directed at precisely this endeavor. The aim of this discussion is to explore the manner in which this is accomplished, using an example to highlight the various requirements of the cognition module from a functional standpoint as well as the neuroanatomy and neurophysiology underlying these requirements when this is known. Ultimately, we will return to the common problem mentioned in the opening of this section of the chapter above in tying the use of the skill sets used in the cognition module to problem solving in everyday life. However, to begin, we envision an individual beginning the cognition module at Level I with the object stimulus presented being a No. 2 pencil. One set of the many appropriate responses for the individual to give would be that the pencil is yellow, cylindrical, composed of wood and graphite, 8 inches long with a diameter of 1/4 of an inch, a few ounces in weight, smoothly textured, possessed of an eraser, and used for writing. The question relevant to this discussion is what cognitive processes are required in order to generate these responses and what are the neuroanatomical underpinnings of those processes.

One of the most basic cognitive processes requisite to success in completing the cognition module is attention. In order to adequately perceive and identify features of an object, it is first necessary to attend to that object in a selective fashion. This concept has been labeled *selective attention*. Specifically, in our therapy task, the individual would be required to selectively attend to the stimulus presented (the pencil) to the exclusion of various other stimuli that might be present. In addressing each specific feature identification task, the individual must selectively attend only to those stimuli that appear relevant to this task. This type of selective attention has been described as being determined by the processes of competitive selection and top-down sensitivity control.[135]

Attention, as a critical cognitive process, has been of great interest to cognitive neuroscientists, and many attempts have been made to elucidate its neuroanatomical and neurophysiological correlates. The results of these studies have indicated that attention is a process that is mediated by widely distributed neural structures. Attention is dependent upon arousal/vigilance, which is subserved by the ascending reticular activating system. Selective attention appears to be mediated by the thalamo-frontal gating system, the PFC, the anterior cingulate (executive attention, attention during auditory processing), the parietal lobe cortex (attention to location), and the occipitotemporal cortex (attention to color/form).[136–138] What has been traditionally referred to as Treisman's spotlight seems likely to be mediated by the pulvinar complex, a nucleus in the thalamus that has projections to the posterior parietal, temporal, and prefrontal cortex, in addition to secondary visual areas.[138,139] The hypothesis is that the pulvinar mediates a top-down influence on cells in various regions, specifically by imposing bias criteria upon cells that respond to a particular stimulus. The influence of the pulvinar has been most explored in relation to the visual and spatial attentional systems. However, the manner in which the pulvinar complex becomes tuned to a particular task demand remains unresolved. In addition to the pulvinar complex, the posterior parietal cortex also appears to be implicated in the process of competitive selection and is another area likely involved in top-down influences on attention.[135,140] Information about the relative salience of stimuli may be encoded elsewhere. Encoding of the relative salience of visual field stimuli, for example, appears to be located in the lateral intraparietal area.[135,140–142]

Thus, attention appears to be a widely distributed process anatomically. The PFC seems to be the most consistently activated region during attention tasks, but other regions mentioned may also be activated, depending upon the specific task at hand and the type of information involved with the task (i.e., visual, spatial, auditory, executive, etc.). There are also important neurophysiological correlates for attention. Specifically, the catecholaminergic neurotransmitters, dopamine and norepinephrine, are thought to modulate processes of attention.[143] Further evidence that these neurotransmitters play an important role in attentional processes is the impact of noradrenergic and dopaminergic medications on attention.

Bringing the discussion back to the example above, the individual would be charged with the task of attending to the pencil in very particular ways in order to discriminate its perceptual features. In determining its shape, for example, top-down processes arising from such areas as the PFC, the pulvinar complex, and also from other regions or networks that have not yet been elucidated would establish the bias criteria for salience of information being presented. In this case, because the information refers to shape, the occipitotemporal cortex is likely to be involved in attending to this specific type of information. Based upon the bias criteria imposed, specific cells programmed to respond ideally to the form presented by the pencil would be preferentially selected for firing, thus making them more effective in competitive selection, and more likely to enter working memory as salient information to the task of determining the perceptual feature of shape for this object.

Working memory and attention are processes that are inextricably interrelated by virtue of their influence upon one another. Thus, no discussion of one can be complete in the absence of the other. Just as the individual must attend to the stimulus in a manner appropriate to the completion of each aspect of the feature identification task, so must he or she hold the information garnered in working memory for use in interpreting results, modifying a perceptual search pattern or strategy or monitoring progress through the module. To be more explicit, the individual must hold the perceptual information acquired with regard to the specific stimulus of the pencil in working memory. He or she must simultaneously hold information about which perceptual feature is currently being identified, which features have already been identified, and which must still be identified. This information is then used not only for the generation of responses to the cognition module task, but also, obviously, must impact the attentional process as well.

Neuroanatomical substrates of working memory have been studied extensively in the field of cognitive neuroscience. The most frequently cited area of interest with regard to working memory is the PFC, and indeed, data from studies in both humans and nonhuman primates support the PFC as a relevant area of involvement.[138] However, additional areas also appear to be important in working memory, and it is becoming increasingly recognized that working memory, like attention, is a widely distributed process and relies on such structures as the inferior temporal cortex and medial temporal cortical areas (including the hippocampus, parahippocampal, perirhinal, and entorhinal cortices), the posterior parietal cortex, the inferior parietal cortex, and higher order areas in the occipital cortex in addition to the PFC.[135,144,145] Data from fMRI studies show that tasks involving working memory consistently activate both the dorsolateral PFC and the posterior parietal cortex and that reciprocal pathways exist between these two areas.[135,146,147] The inferior temporal cortex has been demonstrated to be of importance with regard to short-term retention of visual object features.[148] The medial temporal cortical areas appear to be relevant to working memory, particularly in the maintenance of visual objects when distraction is present as well as for complex novel objects, faces, or scenes.[145]

The processes of attention and working memory are not only interrelated, but also are mediated by many of the same neural structures or networks. This is consistent with the finding that damage to the frontal lobes impairs the ability to balance between environmental events and current goals as this inability could, in essence, be a manifestation of disruption of either process.[146] An individual performing the tasks involved in the cognition module would require effective synergy between the interrelated processes of attention and working memory. Selective attention would be subject to modification via top-down processes influenced by working memory. To give a concrete example, if we suppose that the individual has responded to the perceptual feature of construction but not yet to size, then we can reason that within working memory must be information regarding the next perceptual feature to be described (size) as well as those that have already been described (color, shape, construction) in addition to the perceptual feature information that has been gathered about the object already (the object's name, its color, its shape, and its construction). Presumably, the influence of this information contained in working memory would serve via top-down processes to influence attention and provide a bias for those attributes of the object that would facilitate identification of the size. However, merely attending to and placing the perceptual information into working memory will not alone be sufficient for the individual to accurately determine the features of the object.

In order to accurately identify the perceptual features, the individual must also bring prior knowledge to bear, which leads to a discussion of long-term memory systems, including episodic and semantic memory.[147] In this case, the individual would need to draw from either episodic memory (i.e., a specific past experience with a pencil, the color yellow, a cylindrical shape, a wooden object, etc.) or semantic memory (generalized knowledge about pencils, the color yellow, cylinders, wood, etc.) in order to make sense of the perceptual information at hand. This is to say that mere perception alone is insufficient to produce the desired recognition of the perceptual features of the object. Rather, the individual must draw on some previously encoded information in order to convert the perceptual information to meaningful features. As is discussed later, both episodic and semantic memory have implications for the process of categorization.

Episodic memories are encoded and retrieved through various neuroanatomical mechanisms. Most studies addressing encoding and retrieval have focused upon the PFC and the asymmetrical involvement specific to these two processes. According to the hemispheric encoding retrieval asymmetry (HERA) model, the left-sided PFC is more involved with encoding whereas the right side is more involved with retrieval.[148] However, this has been called into question as some studies have demonstrated bilateral activation during retrieval.[149] The retrieval of episodic memories appears to be distributed fairly widely throughout the brain. Areas of relevance in retrieval of episodic memories include the hippocampus and parahippocampal gyri with some debate about lateralization, the parietal (specifically, the posterior medial parietal cortex), inferior temporal and occipital cortices, the cingulate cortex, and the thalamus.[149] The hippocampus appears to be important in topographical memory formation, memory for faces, and memory for complex colored pictures.

Semantic memory appears to be stored in various regions of the brain that are dependent upon the attributes of the particular unit of knowledge. Evidence for this stems from the recognition that injury to specific regions can produce relatively focal agnosias wherein specific types of semantic information cannot be readily accessed but other types of knowledge are unaffected. One such example is prosopagnosia, which follows damage to the fusiform face area.[150] Similarly, many other selective agnosias have been described including apperceptive, finger, landmark, somatosensory, topographic, and visuospatial agnosias.[138] Particular regions appear to be critical to accessing stored semantic information. These regions are somewhat specific to type of information as well, and in fact, some regions may underlie the specific agnosias although the specific neuroanatomical correlates of the various agnosias mentioned have not been specifically identified. Among the regions implicated in semantic memory are the inferior parietal lobule, the fusiform gyrus, the middle temporal gyrus, the inferior frontal gyrus, the dorsal premotor cortex, and the retrosplenial cortex.[151] There is a general propensity for left-sided involvement compared to right in terms of semantic retrieval. Brain imaging studies evaluating various domains or types of semantic knowledge have demonstrated different brain activation patterns. The most consistent difference in brain activation has centered upon the discrimination between living and nonliving stimuli. The results indicate

the semantic information pertaining to the living stimuli being correlated with activation in the lateral fusiform gyrus whereas that correlated with the nonliving being localized to the medial fusiform gyrus.[151] Another distinction has been identified between motor-based knowledge and knowledge of abstract properties with motor-based showing activation more in the left frontal parietal network (the intraparietal sulcus, inferior parietal lobule, dorsal premotor cortex), and the abstract knowledge showing more activation in the retrosplenial and lateral anterior inferotemporal cortex.[151]

In addition to the neuroanatomical correlates of memory formation, there are important neurophysiological mechanisms involved, including LTP. A detailed discussion of LTP is not warranted here, but a few points are highly relevant. LTP is involved with synaptic consolidation in the hippocampus, is dependent upon the N-methyl-D-aspartate (NMDA) receptor in many instances, and is impacted by the dopaminergic system.[152,153] Some therapeutic interventions aimed at improvement of memory function have attempted to exploit this mechanism using drugs that target the NMDA receptor, such as Memantine, although the efficacy of these efforts has yet to be fully determined.

As the individual progresses through the levels of the cognition module, the stimulus presented for feature identification progresses from the tangible object presented in Level I to a photograph, line drawing, written, and finally, spoken word. Each of these transitions occurs in order to introduce cognitive distance, which forces the individual to rely to greater and greater extents upon visual imagery and prior semantic or episodic knowledge, as discussed previously, and, in some cases, working memory.

The neuroanatomical underpinnings of visual imagery are still poorly understood. The traditional understanding of visual imagery is that the image is displayed in the same sensory cortices in which it was perceptually processed. Thus, visual images have been traditionally thought to be displayed in the topographically organized visual cortices in the occipital lobe. However, there is some evidence that indicates that this picture is incomplete and suggests the involvement of other regions. Neuroimaging studies have demonstrated that visual imagery depends upon large networks that involve the frontal and parietal lobes as mediators of top-down influence upon the temporal lobe.[154] The area of the left temporal lobe appears to be of particular importance, and lesions in this area, when occipital cortex is spared, have produced cases of impaired visual imagery with relatively preserved perceptual function.[155] Given that the contrary dissociation has also been observed with pure occipital lesions leading to cortical blindness or impaired perception with preserved visual imagery, the combination seems to indicate a likely dissociation in neuroanatomical bases for the two processes. There is also evidence that mental images are formed based upon categorical relationships, stored predominantly in the left hemisphere, between particular features of the object, which are encoded diffusely, potentially according to the traditional view of imagery in the analogous regions to the initial perception of such an object. This evidence comes from a case of a split-brain patient who demonstrated impaired mental imagery for stimuli presented to the left hemisphere with relatively preserved imagery for stimuli presented to the right hemisphere.[155]

As the individual progresses through the cognition module, categorization becomes a critical component of performance. This requirement is introduced first in the form of naming additional objects in each feature identification task, then eventually, by the generation of category names specifically. To give a specific example, the individual might be presented with nine objects: three of which are used for writing, such as a pencil, pen, and crayon; three of which are red, such as a stop sign, an apple, and a rose; and three of which are spherical, such as a baseball, an orange, and a globe. The individual's task would be to identify the similarities between the objects, namely that they share function, color, and shape, respectively.

Categorization is also a process that is diffusely mediated. It is a complex process that has intricate interrelations with the other processes reviewed in this section. It is not surprising, then, to discover that many of the same regions are involved in this aspect of cognition. Evidence for the neuroanatomical correlates of categorization are based primarily upon lesion and image studies and are somewhat limited. A more detailed discussion of the theoretical models of categorization is provided elsewhere, but a limited review reveals several areas of importance to this discussion. Different types of categorization appear to be mediated by different anatomical constituents. Exemplar similarity categorization is dependent upon explicit memory and has been demonstrated to involve medial temporal and diencephalic structures.[71] The dorsolateral prefrontal cortex has also been implicated in rule-based categorization, particularly when task switching is involved.[71,78] Category naming tasks demonstrate activation of the left hemisphere angular gyrus[78] or, if they are presented in picture form, the occipital cortex.[155] Generally speaking, the left hemisphere appears to be important in categorization relative to the right hemisphere. Left anterior hemisphere lesions lead to rigid categorical boundaries consistent with impaired cognitive flexibility observed with injury to the PFC.[91] Left posterior hemisphere lesions lead to weak categorical boundaries[94] and inability to categorize pictures or words.[92,93]

Now that we have characterized the underlying neurobiological systems that are implicated in the task of the cognition module, what follows is a theoretical discussion of how these structures relate to the goal of therapy, namely problem solving. To explore this, we return to the opening example and discuss the complex interplay between the various cognitive systems involved. This example is intended to be illustrative rather than complete as this example could be discussed at length in this context.

In the case of an individual who has dropped car keys between the seats, it is easy to demonstrate the complicated manner in which these systems are involved, influence and

are influenced by the other systems, and mediate everyday problem solving. Beginning at the outset of the event, attention must be directed to what has happened in order for a problem to be recognized. Attention to the event and the subsequent task of recovering the keys must be maintained throughout the process. In addition, attentional processes must be modified over the course of the recovery in order to adjust to different needs. For example, in the first case, working memory must be involved in order to store the properties of the various objects involved and their relationship to one another. The properties of the keys, for example, must be attended to and held in working memory so they may be assessed for salience. In this case, their size, weight, and construction might prove to be useful, and so they must be selectively attended to and then held in working memory. If the strategy for recovery were to include the use of a magnetic object, then construction would become a particularly salient feature. If the strategy were to lift or push the keys free, then the size and weight would become most salient. Information gathered by the individual that has importance for which of these strategies is preferable must also be held in working memory and would be used in order to modify the attentional process to refer to these particular perceptual features.

In this case, assume that the strategy chosen is to push or lift the keys free. In this scenario, what becomes necessary is to determine which attributes of an object would be required for success, assess the attributes of an object that might be used to achieve this task, and determine whether these attributes fulfill the criteria required for success. Specifically, the task involved here might require an object that is sufficiently long to reach the object, thin enough to fit in the space between the seats, and sturdy enough to lift or push the keys free. In determining this set of requirements, the individual must attend to and hold in working memory the salient perceptual features of the space between the seat and the center console as well as the keys themselves. When assessing a potential object, top-down attentional control systems must be used to modify the attentional system, increasing the salience of these features to the exclusion of other stimuli. Retrieval of semantic and episodic memories will also inform the individual of potential objects and their attributes that may not be directly available to the individual's sensorium. For example, the individual might recall from semantic memory stores that a No. 2 pencil is long, thin, and relatively sturdy and from declarative memory that one was placed in the glove box yesterday. Obviously, visual imagery is inherent to some of these processes as well. Last, categorization could impact the process via the use of previous categorization to produce suitable (i.e., long, thin, sturdy) objects.

Throughout the problem-solving task, then, it is apparent that various cognitive systems are implicated along with their various neuroanatomical and neurophysiological counterparts. In reviewing these counterparts, it becomes clear that such a task involves widespread structures, not all of which have been fully elucidated. What also seems reasonable, then, is that a therapeutic intervention aimed at remediation of such processes should attempt to recapitulate the process in a systematic fashion. This would involve the various neuroanatomical structures and neurophysiological mechanisms involved, and this, in fact, forms some of the theoretical basis for the cognition module as a therapeutic intervention.

SUMMARY

Cognitive rehabilitation for people with TBI is a crucial component of the rehabilitative process. Although compensatory practices possess some appeal due to the financial and length-of-stay constraints imposed upon treatment, remediative practices should be undertaken for cognitive deficits following TBI. Compensatory strategies may be introduced as tools to supplement cognitive function. Remediative practices must be based upon sound theoretical constructs and be in harmony with known functional attributes of the neurological system. Likewise, cognitive rehabilitation must be approached like any other acquired skill set—that is, hierarchically or developmentally—and incorporate the three basic principles of environmental stimulus, task complexity, and cognitive distance. Finally, broadly based cognitive evaluation should be undertaken before and after treatment to evaluate and document improved function across cognitive domains.

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Principles of cognitive rehabilitation in TBI: An integrative neuroscience approach

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INTRODUCTION

The survivor of moderate-to-severe traumatic brain injury (TBI) is typically faced with an array of neuropsychological challenges. These include cognitive changes in attention, memory and learning difficulties, information processing impairments, executive functioning (EF) deficits, and psychosocial issues, such as emotional or anger management, anxiety, and depression. Neuropsychological deficits often hamper the individual's ability to function independently and return to productive living.[1–4] Subsequently, cognitive rehabilitation (CR) is an integral component of TBI rehabilitation efforts.

Models of cognitive rehabilitation

Cognitive retraining falls under two primary categories: restorative and compensatory. Restorative rehabilitation is based on neuroanatomical and neurophysiological models of learning. These models suggest that neuronal growth and synaptogenesis result directly from repeated exposure and repetition of stimulation through experience.[5] Consequently, cognitive training could potentially lead to the development of new neuronal circuits, which could cause reorganization of partially damaged systems, reduce cognitive impairment, and improve functional ability. It is possible that if rehabilitation is withdrawn too early, then the functional reorganization would not have an opportunity to occur; thus, treatment effects will not be permanent.

The compensatory rehabilitation approach operates under the assumption that certain functions cannot be recovered or restored completely. Therefore, the patient needs to use certain strategies to improve functional performance without relying on the restoration of the damaged neurocognitive systems.[6] The restorative and compensatory approaches could be used together in rehabilitation in order to maximize performance. For instance, assisting the patient to develop self-awareness regarding his or her cognitive needs by the use of systematic strategies could have a restorative effect on planning and deliberate cognitive processing abilities.[6] There are several comprehensive

approaches to cognitive rehabilitation, including works by Ben-Yishay, Prigatano, Wilson and others that focus on holistic rehabilitation,[7–12] and other approaches[13–17] that involve developing hierarchical strategies for the treatment of basic and complex cognitive systems and also helping the patient develop self-awareness and acceptance of changed abilities. The chapter on neuropsychological rehabilitation in this book provides the reader with more in-depth information regarding the scope and objectives of neuropsychological rehabilitation. The present chapter focuses on principles of cognitive organization. The integrative theoretical model presented in this chapter can form the basis for the development of therapy procedures to address cognitive deficits associated with TBI.

Cognitive theory and rehabilitation

Cognitive theory organizes human cognition into a hierarchy of basic and complex processes and systems. Basic processes, such as sensory perception, attention, and memory underlie more complex systems, including categorization, problem solving, reasoning, and abstract thought processes.

Neurobiological research in humans and animals provides support for the cognitive systems generated by cognitive theory. When these networks are disrupted, the observable outcomes include predictable cognitive deficits. The neuropathology of TBI is complex as it consists of both focal and diffuse cortical and subcortical lesions along with a cascade of neurobiological changes. Therefore, unlike unilateral focal brain damage (e.g., resulting from a stroke or a neoplastic lesion), the cognitive disruption observed in TBI can be bilateral and extensive. The challenge of CR is to implement effective and efficient treatment modalities that will enable the survivor to maximize his or her level of functioning in the face of this diffuse systemic disruption.

The purpose of this chapter is to apply cognitive theory, current findings in cognitive neuroscience, and brain research in order to develop principles of CR following moderate-to-severe brain injury. The following questions are addressed:

1. What are the neuropathological mechanisms that affect basic and complex cognitive systems following injury?
2. How does the brain recover from injury?
3. What are the general principles of basic and complex human cognitive systems and how does TBI interfere with these systems?
4. How can principles of cognitive theory be applied to treat cognitive deficits associated with TBI?

EFFECTS OF BRAIN INJURY ON NEURONAL FUNCTION

The most common form of TBI is a closed head injury (CHI). The primary neuropathologies identified in CHI are the result of mechanical forces associated with movement of the brain within the skull. In addition to focal lesions, the inertial loading (due to acceleration or deceleration forces) causes linear and rotational acceleration, which typically coexist or follow each other in CHI[18–20] and may cause greater impairment than do focal injuries at the site of impact. Rotational acceleration forces may have more devastating effects than linear forces because rotational forces lead to greater strain on the axons. The type of strain depends on the direction of the forces applied to the brain tissue. Specifically, tensile forces pull axons apart, compressive forces push axons together, and parallel deforming forces lead to shear strains.[19] Rotational forces may result in focal lesions of midline structures like the corpus callosum and the dorsolateral quadrants of the midbrain. However, it appears that the displacement of the brain tissue and strain rate, relative to the skull, lead to more devastating results than the acceleration per se—that is, a particular group of axons will suffer more damage if strained (or displaced) with more intensity and longer duration than if the same axons were strained at a lower rate of intensity and shorter amount of time. The straining of the axon fibers is one mechanism leading to microscopic damage affecting the soma and the axon and, subsequently, leading to diffuse axonal injury (DAI).[18,19,21]

Cell function/cell death

Upon contact, the individual may sustain a focal injury (coup or contrecoup) and inertial loading due to acceleration–deceleration forces resulting in multifocal and diffuse lesions.[18,19,22] The higher the velocity at the time of impact, as in the case of high-speed motor vehicle accidents, the stronger the inertia forces applied to the skull. The frontal and temporal lobes of the brain, which include systems critical for attention, categorization, strategy building, memory, and learning, are often compromised as a result of coup or contrecoup lesions in CHI. These lesions include contusions resulting from hemorrhagic lesions that can lead to cell death. The mechanism of diffuse neuronal cell loss involves both necrotic and apoptotic neurocascades. Necrotic death is attributed to ischemia (secondary to cell membrane failure), whereas apoptotic cell death evolves more slowly and is not clearly understood.[18,22]

Diffuse axonal injury (DAI)

There is a gradient of injury that occurs both at the axonal level and grossly at the distribution of DAI. The distribution of DAI follows a gradient from peripheral hemispheres to deeper parts of the cerebrum in more severe injuries. In more severe injuries, the corpus callosum and dorsolateral midbrain tend to also be involved—often associated with macroscopic petechial hemorrhages seen on MRI scans.

Studies with animal models and human autopsy findings have been used to study the pathophysiology of DAI.[21,23] Although the discussion on DAI has focused traditionally on myelinated axons, more recently there is evidence

supporting the involvement of fine fiber unmyelinated axons (like the cells found in the splenium of the corpus callosum).[22] Hence, focusing only on myelinated axons may underestimate the full effect of axonal damage. Animal models simulated severe injuries resulting in stretching or compressing of long tract axons with maximal stretching or compression at focal points on the axons' length. At 12–24 hours postinjury, swollen axoplasmic masses, called retraction balls, formed and detached from more distal axonal segments. In less severe injuries, focal alterations of axolemma can lead to progressive changes and a cascade of electrochemical events interfering with axonal transport (anterograde and retrograde), focal axonal swelling, and detachment from the distal axonal segment.

The exact nature of the reactive axonal changes is unknown, but because the effects are delayed, future research might determine how to prevent certain axonal changes. The delayed autodestructive cellular phenomena have been linked to surges of the excitatory neurotransmitter glutamate, especially at N-methyl-D-aspartate (NMDA) receptors. These intracellular surges impede neuronal function. Areas of the brain with large numbers of NMDA receptors, such as the hippocampus, are very vulnerable to the aforementioned autotoxic changes.[19,21] Not all axonal swellings result in retraction balls. In an experimental mild-to-moderate brain injury with cats, some of the swellings showed numerous reactive neuritic sprouts in the brain stem area.[24] By the end of the first month, some of these swellings degenerated, and some continued to mature. Some of these neuritic outgrowths were reorganized to course into the parenchyma (where myelin was absent) or course parallel to the distended myelin sheath.

In the second and third month postinjury, there is great variability in the regenerative responses of animals. Some new sprouting originates from reactive axonal swellings. The more mature sprouting shows further maturation and seems to gain easy access to the rest of the brain.[21,24] It remains unclear, however, whether these neuroplastic changes will yield favorable adaptive or maladaptive changes.[21,22]

During the acute and subacute stages of TBI, Wallerian degeneration, inflammation, apoptosis, excitotoxicity, and prolonged hypoperfusion result in white matter and gray matter volume loss.[25–27] Areas of gliosis are observable in MRI scans of patients with severe TBI. Neuroimaging studies demonstrated that these effects extend beyond the first year, and individuals with TBI exhibit significant brain volume loss in both the subacute and chronic phases.[28–31] It is now understood that such brain atrophy continues for years after the injury.[28,32,33] Findings in our lab at the University of Cyprus indicate that patients with moderate-to-severe TBI studied at a median 6 years postinjury sustain significant brain volume loss (gray matter and white matter) that is associated with the chronic neurocognitive sequelae. Participants with TBI, when compared to a matched group of neurologically healthy participants, exhibited significant cognitive deficits and substantial reduction in both gray matter and white matter volume. Gray matter volume was reduced by a mean of 9.60%, and white matter volume was reduced by a mean of 7.04% in the TBI group compared to the control group. The substantial volumetric differences between the TBI and the control groups suggest that the injured brain remains malleable for many years following the injury.[32] Using voxel-based morphometry, such significant volumetric differences were found to be mainly concentrated in orbitofrontal and temporal cortices, the cerebellum, and other areas connected to the thalamic network (i.e., putamen and insula).[34] These results are consistent with a multitude of previous evidence on the pattern of brain atrophy in the acute and subacute phases of TBI.[30,32,33,35] Previous research findings indicating that frontotemporal and subcortical thalamic networks are more vulnerable to TBI, when taken together with our findings that a similar network of brain areas exhibits significant atrophy during the late chronic stages of moderate-to-severe TBI, support the thesis of TBI as the initiation of a chronic disease with long-lasting effects on the brain rather than a single event with a static course.[28,35,36] This cascade of neurodegenerative events could lead to early pathological aging and is considered to be a significant risk factor for dementia.

Metabolic dysfunction

The mechanical and cellular changes, described previously, can lead to a wide array of metabolic changes. Similar to the aforementioned changes, the metabolic cascade can also be focal, multifocal, and/or diffuse. Even persons with mild brain injury are extremely sensitive to slight changes in cerebral blood flow (CBF), increases in intracranial pressure, and apnea. Although advances in technology, such as PET, diffusion tensor imaging (DTI), NMR spectroscopy, and microdialysis studies, have been extremely helpful in understanding the metabolic effects of TBI, the exact mechanism of this injury-induced vulnerability is not fully understood. It appears that this metabolic imbalance is heterogeneous and affects brain areas differently. The metabolic cascade has become a major concern in brain injury management as it can lead to further tissue damage and contribute more extensively to the neurobehavioral outcomes following TBI than the initial mechanical damage.[37–40]

This vulnerable state following injury is thought to be a result of interactive neurochemical and metabolic cascades following injury, consisting of several mechanisms that are described in experimental and human brain injury:

1. A massive release of the excitatory neurotransmitter glutamate leading to excitotoxicity and also to an increase in glucose metabolism (hyperglycolysis)—the temporal lobe and hippocampal areas are particularly vulnerable to the glutamate surges.[22,24,41]
2. Ionic fluctuations, such as increased levels of extracellular potassium (K+)—the increase in K+ activates the ATP-dependent sodium–potassium pumps and results in considerable metabolic stress and possibly hyperglycolysis.

3. Elevation in extracellular calcium (Ca^{++}) has been shown to increase vasoconstriction, which may account for the reduction in CBF and may also activate destructive lipases and proteases.[41,42]
4. Production of reactive forms of oxygen species that cause damage via the induction of lipid and oxygen oxidation.
5. Loss of autoregulation as evidenced by increased demand for glucose (hyperglycolysis) lasting from immediately after and up to 1 week following the injury[21,41,43] and a reduction in CBF.
6. The acute period of hyperglycolysis is followed by a period of metabolic depression and reduction in glucose utilization (i.e., hypoglycolysis) that lasts for up to 10 days in experimental TBI.[43] During this period of time, there is a decrease in protein synthesis and oxidative metabolism, which suggests that the glycolysis is not the only metabolic pathway affected in brain injury.[22]

Brain reorganization and sprouting following injury

In the central nervous system, when neurons are killed or when axons are damaged, the axon terminals of those cells will degenerate, thus, vacating synaptic contacts on postsynaptic neurons. The postsynaptic cell will die if enough of its presynaptic contacts are vacated. If the postsynaptic cell survives, its soma and/or dendrites will have vacant locations where presynaptic degeneration has occurred. At this point, a number of possible events can occur that can result in recovery of function. The damaged axons can regenerate and form new terminals on the cells they previously innervated, or axons from other neurons can sprout new terminals that form synapses at the vacant locations on the postsynaptic neuron. This sprouting constitutes a reorganization of the connections among the surviving brain structures and can serve as a major impetus for recovery of function. All sprouting is not, however, necessarily adaptive. As mentioned previously in this chapter, it is possible for the newly sprouted connections to result in maladaptive behaviors.[44]

The reorganization of the brain by axon terminal sprouting is not unique to the aftermath of neuron death in the brain. It occurs naturally in the healthy brain continually during development and later in life. During development, axon terminals compete for positions on various somata or dendrites of neurons. Similarly, when an otherwise healthy neuron looses synaptic contacts on its soma or dendrites, a variety of different afferent cells will compete for the vacant areas on its surface. The nature of the connectivity of the "recovered" brain should be very dependent upon the particular pattern of new synapses that form.

During development, it is clear that the patterns of connections that form and prevail are severely impacted by the nature of the organism's experience. For years, it has been known that there are gross differences in brain structure as a result of different experiences. Later studies have shown that the structure of individual neurons in the neocortex is dramatically affected by experience. A good example is shown in the studies of the brains of animals raised in enriched versus impoverished environments. Animals raised in an enriched environment have neurons with richer dendrite trees, containing a larger number of higher order dendritic branches and more synaptic contacts. These observations were first made in young animals, but have been shown to occur in adult animals as well. In fact, the richness of the connections of various neocortical cells will rise and fall in very short intervals with changes in inputs to those cells.[45] The particular pattern of new connections following brain damage should also be dramatically affected by the experience of the individual during recovery, following the lesion. And some patterns may prove to be detrimental to the organism. The issue for rehabilitative therapy is to determine the patterns of experience that best optimize posttraumatic performance.

One of the most frequently used procedures to study synaptic plasticity examines the effects of repeated stimulation of the presynaptic cell on the excitability of the postsynaptic neuron. Depending on the parameters of the repeated stimulation, such stimulation frequently results in "potentiation" or "depression" of synaptic efficacy. Earlier studies revealed that changes in the excitability of the postsynaptic neuron lasts for minutes and is called short-term potentiation or short-term depression. However, later studies revealed that, at certain synapses, such changes could persist for longer periods of time—in some cases for many days. Changes in synaptic efficacy that are seen following long-term potentiation and depression can result from an increase or a decrease in the amount of neurotransmitter released from the presynaptic terminal, an increase or decrease in the number of active postsynaptic receptors, the sprouting of new synapses, the pairing down of existing synapses, or changes in the structure of existing synapses, such as changes in the size or shape of dendritic spines or modification of the synaptic cleft.

At present, theories of the changes in cell interaction induced by experience or recovery following brain damage focus on changes in the properties of existing synapses or the sprouting of new synapses between cells that already have direct synaptic contact. However, during development, changes in brain function and organization are attributed to the formation of new synapses between cells that did not previously interact. Clearly, before Purkinje cells exist in the cerebellum, there can be no synapses between climbing fibers or granule cell parallel fibers onto Purkinje cells. Obviously, the birth of new neurons that form functional synapses with other neurons requires one to address the issue that synapses must be forming between cells that previously had not interacted.

In spite of the remarkable degree of behavioral and cognitive changes that accompany adult learning and memory or recovery of function, most cellular models of neural plasticity do not consider these changes to be accompanied by synaptogenesis between previously noncommunicating

neurons. The theories generally assume that the new synapses that are formed during learning or recovery only strengthen (or weaken) communication between already communicating neurons. This position has not been challenged because of the dogma that no new neurons are formed in the adult brain.

Exciting experiments in the past two decades have demonstrated that new neurons continually form in the brain of adult animals, including primates and humans.[46–50] New neurons were first found in the brains of adult songbirds in areas of the brain associated with song production. Then, new granule cells were found in the hippocampus of adult chickadees; then, in rats and primates.[47] The same pattern of neuronal generation has been found in the hippocampus of adult humans.[46,48] Recently in monkeys, new neurons were found to be migrating to the neocortex from stem cells in the region of the ventricles.[50] Adult neurogenesis results in continual influx of neurons that are (temporarily) immature and, therefore, structurally plastic. The hope is that the immature cells can take on functions of mature, adult cells. Although this premise has not been verified yet, adult neurogenesis can have important implications for our understanding of the mechanisms of neural plasticity in general and recovery of function following brain lesions in particular.[46,49,51]

Relating to the discussion of reorganization and recovery of function, a multitude of research studies have demonstrated that TBI results in heterogeneous patterns of recovery among patients who sustained similar types of injury. Concepts such as brain reserve and cognitive reserve have provided some explanations for these phenomena. Although these constructs are related, they are not synonymous. Brain reserve is defined as the brain's capacity to sustain a certain amount of pathological change before the emergence of the associated clinical symptoms, and it is measured by anatomical indices, such as total intracranial volume, head circumference, and ventricle-to-brain ratio.[52,53] On the other hand, cognitive reserve is a psychological construct, and is defined as the ability to use alternate cognitive strategies in order to optimize or maximize performance on cognitive tasks. It is formulated by lifetime indicators, such as years of education, semantic knowledge, and reading abilities as well as socially and cognitively engaging leisure activities.[54–56] These two constructs may explain, in part, the differences in recovery patterns during the acute and chronic phases of recovery, among TBI patients who sustained similar types of injury.

In summary, the aforementioned effects of cell injury, DAI, and metabolic dysfunction and the ability of the brain to withstand pathology and reorganize contribute to the morbidity and severity of neurobehavioral outcomes for several years postinjury. During the acute phase of injury, as the metabolic balance returns to premorbid levels and neuronal reorganization takes place, the patient's clinical picture begins to evolve, and the long-lasting effects of the injury become evident. The following section will present general principles of cognitive theory and the effect of injury on those systems.

GENERAL PRINCIPLES OF COGNITIVE SYSTEMS

Perhaps the most influential guiding principle of modern cognitive neuroscience is the concept of modularity. Early in the history of cognitive psychology, modularity referred to the strong claim that specific faculties could be completely delineated into separate neural areas.[57] This very rigid view of local representation of function was contrasted with the neo-Lashley hypothesis that computation is distributed across large neural populations and that whole patterns of neural activity, modeled in devices referred to as neural networks or parallel distributed processing systems, constituted states of cognition.[58] When taken to the extreme, the distributed processing approach spawned a model of brain function that was holographic in nature.[59] The truth, not surprisingly, lies somewhere in between these two end points, and today, most cognitive neuroscientists adopt a "weak" modularity framework to describe cognitive processing in the brain. Weak modularity holds that the simple computations and their underlying neural substrates are relatively localized and loosely autonomous.[60] Responses of neurons within these systems are tuned to specific characteristics in the environment, but that tuning is broad (i.e., the response of the cell falls off gracefully when the stimulus departs from the cell's preferred stimulus).[61] Complex cognitive activities are accomplished by the coordination and communication among these more specialized modules. Basic processing principles governing how processing takes place appear to hold across systems, and these principles may be formulated in terms of computational styles or strategies—that is, cognitive activities spanning a variety of tasks may be rule-governed, similarity-governed, or, through extensive experience or preexisting propensities, be automatically accomplished. Characteristics of the environment, the task demands, and the individual all play into which processing strategies and systems are utilized.

The implication of this framework for cognitive psychology has been to redirect research to identifying and characterizing functional systems and their basic components. In addition, investigators now also search for basic processing principles and hold across different functional systems that may dictate how different situations lead the brain to recruit different processing strategies. Methodologies from both traditional cognitive psychology (involving behavioral measures of accuracy and response times) and modern cognitive neuroscience (utilizing brain imaging and lesion/damage dissociation logic) have been brought together in identifying major systems and their processing characteristics. The following sections review the basic cognitive systems (attention, memory, and language). Each of these may be broken down into even smaller functional units as well. Examples of their coordinated deployment in higher cognitive tasks

are described to highlight the interactive processing so central to the weak modularity hypothesis.

Domains of cognition

ATTENTION

Various organizational frameworks have been proposed to understand the concept of attention. One of the more prominent, due to Posner and his colleagues,[62] divides the attentional system into three separable but interacting networks: alerting, orienting, and executive control. The existence of these three systems illustrates the principle of modularity that is central to the cognitive neuroscience approach: They can operate independently and be selectively influenced (e.g., impaired) but are usually coordinated in complex cognitive tasks.[63] More recent work, reviewed in Peterson and Posner,[64] has further delineated these attention networks into subnetworks as well as illuminated the brain mechanisms underlying their operation. This overall framework has also motivated an assessment paradigm, the attention network test (ANT)[65] that has become increasingly prevalent in clinical evaluation.[66]

Alerting network

The concept of alertness has both the notions of bringing to awareness the outside world and the maintaining of an aware, engaged state of mind over a longer time interval. A warning signal in the environment produces a phasic change in alertness prompting the organism to go from a resting state to a state of preparedness.[67] This alerting function enables enhanced processing of an expected event.[64,68] One suggestion is that the phasic change in alerting when a warning signal occurs suppresses the default mode network, a group of brain structures whose activity is highly correlated and enhanced during resting states.[67,69] Properties of the default mode network have been related to attention performance after TBI,[70] clinical pathology such as schizophrenia,[71] and even academic performance.[72]

Many tasks in the real world require not only a phasic change in alertness due to a prompting event, but also the maintenance of vigilance and sustained attention post target in the performance of a task over time, termed intrinsic alertness,[73,74] to capture the notion of alertness in the absence of external signals. Lesion and imaging data implicate a mostly right lateralized network of structures subserving intrinsic alertness (vigilance) that includes the locus coeruleus (the source of norepinephrine, the neurotransmitter responsible for arousal and alertness), dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC), inferior parietal (IPC), and thalamus[74,75] with strengthened contributions of DLPRC and some parietal areas in the left hemisphere[63] when phasic changes in alertness are prompted by an external warning signal. Traumatically brain injured individuals who also sustain right frontal damage have difficulty in sustained attention tasks. Robertson et al.[76] looked at a sustained-attention-to-response-target task in brain-injured subjects compared to controls. The authors found that TBI patients showed a significantly reduced tendency to slow down their responding after an error when compared to controls and had greater variability in response times. In addition, Robertson et al. found that variance on the sustained attention to response target task strongly correlated with informant report of daily life attentional failures in the TBI group.

Orienting network

Orienting refers to the prioritization of specific locations in the environment that results in the enhanced sensory processing of objects in those locations.[77] Orienting can come about from either the volitional (top-down) control of attention to those prioritized sites in the service of a task goal or as a result of an external attention-attracting stimulus that draws one's awareness independent of current goals. Research in attention has established that two relatively separable but interacting networks subserve each of these different functions.[64,78,79] The voluntary control of attention is governed by a dorsal attention system that recruits dorsolateral prefrontal cortex, frontal eye fields, and regions in parietal cortex. This frontoparietal network is topographically organized, has an egocentric frame of reference, and spans across both hemispheres, each of which represents contralateral space. In contrast, the attention system that responds to exogenous cues occurring outside of the current focus of attention (loud noises, sudden onset of brightness) is mostly lateralized to the right ventral areas of frontal and parietal (e.g., near temporal parietal junction) cortices and does not seem to possess a spatial or topological organization.

Much of our early knowledge of attentional orienting derives from observations of individuals with the clinical syndrome of spatial neglect usually occurring as a result of focal injury (e.g., stroke) most often in the ventral regions of the right hemisphere. Symptoms of neglect include a severe bias of attention toward the side of space ipsilateral to the lesion. Numerous studies have clearly documented this deficit as one of attention rather than perception.[80]

Corbetta and Shulman[79] advanced compelling arguments for the view that the dorsal and ventral attention systems must interact to produce the phenomena of neglect. Spatial neglect occurs only when the ventral system is lesioned, yet this system does not directly subserve the functions that are impaired in the clinical syndrome of neglect. Those properties of spatially organized attention control and egocentric bias are hallmarks of the dorsal system. Yet, dorsal lesions do not cause neglect. The paradox is resolved by recent evidence that demonstrates an interaction between arousal (attributed to the right hemisphere) and control of spatial attention. When healthy individuals have low arousal, they will bias their attention to the right visual field, and increases in arousal can reduce the degree of neglect in right hemisphere lesion patients.[81,82] Nonspatial deficits occurring in neglect (reduced vigilance, slowness) resemble issues in arousal and alerting and are becoming increasingly important in the clinical understanding and treatment of this pathology.[83]

Executive network

Executive function (EF), discussed in more detail in the following section, refers to the collection of processes whose execution and coordination are necessary for the success of goal-directed behavior.[84] The executive network of Posner's tripartite attention system may be the core component of this collection serving as the supervisory control structure. This network is also referred to as the central executive in working memory models,[85] the anterior attentional network,[86] and the controlled process of short-term memory (as opposed to automatic process).[87,88] This system is largely responsible for activating a dynamic mental representation of the current situation, ensuring that important relevant features of that situation are amplified[89] and selecting the most appropriate response from among a set of competing alternatives. Its signature feature is the ability to inhibit prepotent responses, allowing the most goal-appropriate behavior to proceed. More recent views of the executive control suggests that there may actually be two separable networks that could operate independently: a lateral frontal–parietal system that activates goal-relevant mechanisms at the beginning of tasks, allowing for task initiation and switching, and a medial frontal–cingulate system that supports a sustained focus on the task situation over time and conditions.[64,90]

Attention network test

Assessing the efficiencies of each of these proposed networks was made possible by the development of a cognitive task whose trial structures allows for separate measures of response time and accuracy to be computed.[65] The Attention Network Test (ANT) requires one to indicate which direction, left or right, a central arrow is pointing by pressing the appropriate key. Trials differ according to the presence or absence of a pretarget cue (and its nature) and the direction of flanking but irrelevant arrows. Specific comparisons across these trial types permit the measurement of each network's efficacy (e.g., cued vs. uncued indicates alerting efficiency). Imaging results utilizing this task have provided evidence to support the anatomical organization of each network.[63,91] Application of the ANT to clinical pathologies includes the assessment of adolescent psychopathy,[92] TBI,[93] aging and Alzheimer's,[94] attention-deficit disorder,[95] and schizophrenia.[96] Some concerns regarding its reliability have been expressed.[63,97,98]

Following moderate-to-severe TBI, increased attention requirements could result in cognitive fatigue, resulting in attentional failure. Survivors of brain injury may experience an inability to maintain attention and discriminate in the presence of distractors (e.g., vigilance) as well as difficulty in shifting between targets. Clinical assessment will often reveal a pattern in functional inconsistencies. These inconsistencies in functioning may leave TBI patients with a sense of vulnerability to circumstances that they don't understand and can't control, especially during periods of fatigue, pain, distractions, and excessive task demands.[99–102]

CR of attentional processes attempts to recognize and control potentially adverse personal and environmental conditions and train patients to become more resistive to distracting situations. The ability to acquire or learn tasks to an automatic, effortless level appears to be preserved after TBI even though it may take longer and require more practice.[103] TBI patients could be trained to recognize particular situations that may affect their performance and can learn to seek out environments that are more conducive to productivity. In addition to awareness training, another component of attention training is rehearsal. It has been observed that, with practice, the effort and attentional control required for a task will decrease as the task becomes more automatic and efficient.[101] Therefore, it is important to train a patient to perform functional tasks, rehearse them in order to improve accuracy and efficiency, and decrease the amount of mental effort. Attention retraining should also challenge the individual by systematically increasing the level of distractors to simulate real-life demands.

In their Attention Process Training (APT) program, a component of a hierarchically organized process-specific approach to cognitive retraining, Sohlberg and Mateer[104] begin with sustained attention tasks. The APT program progresses hierarchically from sustained attention to selective, alternating, and divided attention activities. Attention training has reportedly resulted in improved memory performance in patients with TBI.[104] The reader is referred to Sohlberg and Mateer[17,104,105] for further information regarding this training program. Tiersky and associates[106] used APT alongside of cognitive behavioral therapy to improve coping strategies and reduce frustration in a randomized controlled trial with 20 participants. Patients demonstrated improved performance on complex attention tasks as compared to the wait-listed controls. Attention training that focuses on strategy building, like the APT and compensatory strategy training, seems to be appropriate during the postacute phase when the patient is oriented and able to remember day-to-day information.[107]

MEMORY SYSTEMS AND PROCESSES

Our current understanding of memory suggests that it is organized with respect to both time and contents.[108] On the basis of behavioral evidence[109,110] and neuropsychological data,[111] the distinction between a short-term and a long-term retention system was the first to be made.[87] Initially, the nature of the information handled within these time-delineated systems was thought to be unitary, but a variety of neuropsychological and behavioral findings argued for a content-based subdivision that incorporates multiple memory systems.[112] We present this organization here and discuss its implications for CR following TBI. It should be emphasized that the concept of system organization needs to be supplemented with considerations of memory processes operating across all subsystems, such as encoding and retrieval.[113] The executive network described earlier in the context of attention is deeply involved in these active memory-related processes. Hence, any disruption to the frontal lobes underlying EF will produce impairments in memory tasks, in addition to attention tasks as described

Table 28.1 Memory systems in the human brain

System	Subsystems	Divisions	Function	Brain structures
Working memory	Central executive		Control	Frontal lobes
	Visuospatial sketch pad		Hold visual information	Occipital/parietal
	Phonological loop		Hold acoustic information	Left temporal/parietal
Long-term	Explicit	Semantic	General facts	Temporal
		Episodic	Autobiographical experiences	Medial temporal (hippocampus) diencephalon
	Implicit	Procedural	Motor and cognitive skill	Basal ganglia/motor cortex
		Perceptual representation	Priming/perceptual encoding	Sensory cortex
		Simple associative/ classical conditioning		General, throughout CNS; cerebellum

Note: The term *working memory* has different meanings in different literatures. For example, in animal learning research, working memory describes tasks in which the capacity to hold information across trials within a test session is necessary for performance as in a radial maze navigation task.[114] Baddeley[83] argues that the concept of working memory in this literature probably involves long-term memory as is conceived in human memory research. Yet another approach to the short-term versus long-term distinction argues that short-term, or working memory, refers to traces that are lost if consolidation via the medial temporal lobe system is prevented due to injury or insult.[96] The time scale for this (on the order of 30–40 minutes) is much longer than the very brief duration of short-term memory (on the order of seconds[73]) as considered in cognitive psychology. Within the consolidation point of view, a memory is short-term if its availability still involves the hippocampus, and it becomes long-term as permanent corticocortical connections are formed.

in the previous section. Table 28.1 lays out the current view of the organization of memory in the human (and possibly mammalian) brain.

Working memory systems

When information arrives via the sense organs, i.e., perceptually encoded, it is deposited into an immediate working memory[1] system that is divided into three subsystems specialized for different functions[115]: a control system—the executive network of attention described above and two slave systems each handling different types of information. Visual (e.g., color and shape) and spatial (i.e., location) information is held and manipulated in a visuospatial sketch pad. Cortical areas that are involved in visual perception (the occipital lobe) and spatial orienting (the parietal areas, especially, the right parietal lobe) subserve the operations of this sketch pad.[116,117] Sounds, especially auditory speech sounds, are stored and processed by the phonological or articulatory loop, a term that emphasizes its prototypical activity of recycling acoustic information to keep it in conscious awareness. Baddeley and Wilson[118] proposed a memory buffer mechanism responsible for integrating information between the phonological and visuospatial systems and storing information that exceeds the span capacities of the two subsystems. Recently, Baddeley, Allen, and Hitch[119] reviewed the evidence for this episodic buffer and pondered the neurological underpinnings of this binding mechanism. Although others have argued that the hippocampus plays a key role in this process,[120] Baddeley et al.[119] argued that this may not be the case, and the locus of this buffer is still in question. The existence of this buffer accounts for the fact that some patients may demonstrate intact immediate recall abilities (including supraspan capacities) but impaired long-term memory functioning.[121]

Recall, to work efficiently, the executive network must be flexible enough to switch attention to different aspects of the situation or change response selection strategies as environmental events change. This system is limited, in that there is difficulty in attending to several mental events simultaneously. This limitation goes beyond the interference in attending to multiple aspects of a stimulus due to shared processing pathways in the perceptual system. This capacity, termed working memory capacity,[122,123] varies among and within individuals at different times. Factors such as age, mood, fatigue, and arousal contribute significantly to an individual's effectiveness with controlled operations.[101,124] Studies of the capacity of working memory often use a task in which a sequence of items (e.g., letters or digits) is presented to a subject who must reproduce them immediately from memory in the correct order. The length of the longest sequence (in terms of number of digits or letters) correctly produced, termed the letter or digit span, is an index of the size of short-term memory, which some believe is correlated with IQ measures of intelligence.[125] However, others suggest that this span reflects the capacity of the phonological loop rather than the entire working memory system, and the role of the phonological loop in general cognitive function has been called into question.[123,126,127] True working memory capacity of the executive network that has been shown to relate to higher cognitive functioning[128] is better measured

by tasks that require either dual processing or inhibiting prepotent responses, both activities that are the hallmark of flexible control of attention.[123,129–131] Tests that measure static spans (e.g., forward span of the Wechsler Adult Intelligent Scale [WAIS]) are dissociable from those that measure the more active processes involved in attentional control, such as digit span backward and verbal learning paradigms such as the Rey Auditory Verbal Learning Test or the California Verbal Learning Test.[121,123,132] The loop appears to be necessary, however, for language acquisition, either the early childhood learning of a native language[133] or in adult learning of foreign languages.[134,135]

A growing body of evidence points to the importance of individual differences, especially in working memory capacity, for understanding performance in a variety of cognitive tasks.[136] The individual differences perspective is not news in psychometric research areas, such as intelligence and neuropsychological assessment. A significant body of work points to the clear relationship between one's ability to control cognitive resources and better performance on standard measures of intelligence. For some time, it was paradoxically asserted in the literature that, sometimes "less is more," in that too much working memory capacity may be a hindrance, especially in cases in which learning requires the abandonment of verbalizable strategies in favor of insight.[137–140] However, more recent evidence brings working memory capacity back into its rightful place as the driver of intelligent behavior.[141–144]

Long-term memory: Declarative and nondeclarative

Some incoming information undergoes the process known as consolidation, which results in it being stored in various long-term retention systems. The different routes to storage together with the distinctions among the kinds of information permanently stored define the various hierarchical subsystems of long-term memory. At the top level of the taxonomy adopted by many cognitive neuroscientists[112,145] is the divide between information that can be consciously declared to have been learned or experienced (*declarative* or *explicit memory*) and information whose learning is only reflected by changes in future behavior as a result of the prior experience without conscious remembrance (*nondeclarative* or *implicit memory*). The kinds of items deemed declarative include general knowledge or facts about the world, termed *semantic memory*, and personal, autobiographical recollection of experiences, termed *episodic memory*. Early on, little was known regarding the exact locus of stored memories,[146] but more recent evidence establishes that many properties of the knowledge for facts, events, objects, and actions reside in the very structures that were involved in their original processing[147] with the intriguing proposal of a modality-general "semantic hub" residing bilaterally in the anterior temporal lobes.[148] The idea of a domain-general semantic hub comes from research on semantic dementia, a neurodegenerative disease relatively localized to the anterior temporal lobes. The predominant symptom is the loss of conceptual knowledge that affects all categories and sensory modalities. We elaborate more on conceptual knowledge in a later section. However, based on observations from pathologies, such as semantic dementia, Patterson and colleagues have proposed that the anterior temporal lobes are a modality-independent linking structure that allows for the generalization across concepts so necessary for effective reasoning and language understanding.

Both semantic and episodic memories were thought to require a functioning medial temporal lobe system (hippocampus, amygdala, and adjacent cortex, but especially the hippocampus) for their learning.[145,149] Individuals with medial temporal lesions typically show very little retrograde amnesia; they have excellent memory for most of the experiences that they have had prior to the brain injury with the exception of events immediately preceding insult, perhaps due to their lack of consolidation. However, these patients show profound anterograde amnesia in that they cannot recall new events that they experience after the lesion. They perform poorly on the standard measures of declarative memory, such as recognition and recall of previously studied material. The subject can recall a new experience for a few seconds before it fades, reflecting an intact working memory. All of this early evidence was consistent with the view that the medial temporal lobe was the gateway into declarative memory. There were some contradictory findings in neurological case studies that suggested alternative routes into declarative semantic memory.[150] But these scant few demonstrations were controversial due to variability in lesion extent and methodologies.[151] Rosenbaum et al. review several case studies in which declarative (consciously available) learning was possible even though significant damage to the medial temporal lobe structures thought essential to this type of learning was present. Several key features of the learning experience, however, appear to be necessary for hippocampal independent semantic learning to be possible: The new knowledge must leverage an existing schema in the patient's long-term memory, and the learning task must be engaging and involve active discovery that utilizes the patient's existing knowledge. If these features are present, the learning is enabled although perhaps it is better characterized as incidental.

One interesting research theme that has emerged in recent years concerns the mechanisms underlying the process of retrieval of declarative memories. When probed about a past event, individuals may actually be able to recall the event in detail or may merely experience a sense of familiarity of the event if asked to recognize it. In the traditional view of memory, recall is thought to be the more challenging task, and familiarity without recall is the result of memory activation that falls below the recall threshold.[152] However, recent evidence from clinical lesion cases suggests that two separable mechanisms may actually underlie remember (recall) versus know (familiarity) judgments. Rosenbaum et al.[153] describe amnesiac patient cases that illustrate a double dissociation between recall and familiarity. In many patients with damage to medial

temporal lobe structures, specifically the hippocampus and fornix, recall of memories was greatly impaired while familiarity was preserved. This is the typical result that originally led to the belief that recall was a more powerful form of recognition. However, a more recent case described in Rosenbaum et al.'s review presented the opposite dissociation in which familiarity was impaired but recall was preserved. The areas specifically lesioned included the perirhinal cortex, which sends inputs to the hippocampus. Theories from animal work had suggested that input structures to the hippocampus supports familiarity while the hippocampus itself and its outputs support active recollection.[154]

Implicit memory consists of a heterogeneous collection of various kinds of memory preserved in the loss of declarative memory ability. These systems are quite distinct from one another and rely on entirely different brain structures. The development of *procedural memory* is independent of the hippocampal formation but appears to depend on the basal ganglia, especially the caudate nucleus.[155,156] Procedural memory is typically divided into two major subtypes, which, on their surface, appear to be quite different but appear to depend on the integrity of similar brain systems. One of the major categories is motor skill memory and the other is cognitive skill or reference memory. If an individual learned how to ride a unicycle today and her episodic memory is intact, tomorrow she will report having remembered the experience. However, even if she has no explicit memory of the experience (due to hippocampal damage), she will show intact motor skill memory as manifested by improved performance on unicycle riding. Subjects with lesions invading the motor and premotor areas of the neocortex frequently display difficulty in motor skill learning. Yet, if their hippocampus is intact, they will recall the experience of attempting to ride the unicycle.

Reference or cognitive skill memory, the memory of the procedures that are necessary to win a game or solve a problem, including some kinds of category learning (see the following), constitutes the second kind of procedural memory. This form of memory does not refer to explicit declarative memory for the rules of the game, but refers to the acquisition of successful strategies. An individual with medial temporal lobe lesions could improve their skill at board games, such as checkers, without recalling that they had ever played the game before. Thus, the solution of some complex cognitive tasks does not require explicit memory, but rather repeated exposure to a specific situation and rules for solutions. Quite possibly, the learned strategies are a collection of observations of cause and effects that are reinforced according to the principles of operant or instrumental conditioning. Consequently, patients with TBI may benefit from the repetitive nature of certain activities in CR and become more adapted and independent without necessarily demonstrating improvement in explicit memory tasks. Although both forms of procedural learning involve the basal ganglia, motor skill learning appears to be dependent on the integrity of the motor areas of the neocortex, including the premotor strip, and cognitive skill learning appears to be more dependent on sensory cortices in the parietal and occipital lobes.[155]

Another type of implicit memory is revealed in studies of *priming* phenomena. Priming refers to the facilitation in the processing, detection, or identification of an item as a consequence of its prior exposure in tasks not requiring conscious recollection.[157] A classic priming paradigm involves an initial study of items, such as a list of words, under the guise of some ruse instructions, which is, then, followed with a nonmemory task, such as lexical decision ("Is this letter string a word or nonword?"), word identification ("What is this word?"), or word stem completion ("wo_ _"). The typical finding is that lexical decisions and word identifications occur more quickly or require less stimulus energy to achieve a given level of performance for words previously seen. In the word stem completion task, subjects tend to supply words seen from the earlier list to complete the partial words.[158] That priming is subserved by a different system than explicit memory is demonstrated by several observations although a brain imaging study suggests some involvement of the hippocampus in priming.[159] Individuals with amnesia who fail traditional tests of explicit memory exhibit normal priming[160–163]; individuals with damage to perceptual areas, such as the occipital lobe, show normal performance on explicit measures of memory, but do not evidence priming,[164] and performance on standard recognition and recall tasks can be dissociated from priming tasks in normal subjects.[165–168] Priming appears to be perceptual in nature as any surface change of the stimulus (e.g., font changes for word stimuli or changes in picture orientation for visual stimuli) from prior exposure to test can reduce it[169–173] and is mediated by the sensory cortices (visual priming in visual cortex, auditory priming in auditory cortex, etc.). This system responsible for priming is referred to as the perceptual representation system in Schacter's framework[174] and is the system involved in the initial perception and encoding of a stimulus.

A final category of implicit memory includes simple classical conditioning and associative learning of the sort often studied in animal learning research. These simple forms of learning, evidenced even in invertebrates, may reflect principles of neuronal plasticity in general, such as Hebbian learning or long-term potentiation. However, there is evidence for the special role of the cerebellum in classical conditioning of discrete motor responses such as eye blinks in the presence of air puffs.[146] It is unlikely that TBI would disrupt this form of learning if the patient exhibits any signs of consciousness or has any cognitive functioning at all. Classical conditioning has been demonstrated in decorticate and decerebrate laboratory animals. We mention this type of memory here to provide a complete picture of what is known regarding memory systems.

Role of processes and strategies in memory

The above sections describe different categories of memories, emphasizing the nature of the memory content as

revealed by dissociations of the effects of variables on performance using different types of tasks and materials. However, understanding memory performance requires consideration of the active strategies and processes implemented during the various memory tasks. Most forms of memory assessment especially in clinical neuropsychological contexts rely heavily on explicit measures[84,175] as this type of memory is most characteristic of human cognitive performance and seems to be most influenced by active memory strategies.

Early cognitive studies of memory formation focused on the stage model (consisting of encoding, storage, and retrieval) and argued that certain ways of organizing the to-be-remembered material led to more durable memory traces.[176] If the individual elaborated upon the deeper meaning of items, emphasizing connections to already learned material or involving visual imagery,[177,178] those items would be less subject to forgetting than items merely rehearsed by being recycled in the phonological loop. This idea has been exploited in various prescriptions of strategies to improve memory performance in cognitive rehabilitation.[179–182]

This active elaboration clearly places demands on working memory, especially the executive control component responsible for the planning and sequencing of currently active mental operations. When subjects with CHI were presented with unclustered words (word lists that were randomly organized), they did not actively organize this information according to meaning as did normal subjects, indicating a passive or shallow learning style.[183] Although normal immediate recall is observed in these patients, suggesting an intact auditory span, the reported passive learning style of the CHI subjects reflects an inability to apply active memory strategies, successfully acquire information in the working memory buffer zone, and subsequently move information from working memory to long-term memory, partially attributed to white matter disruption.[184] This difficulty is manifested during demanding tasks, such as the Auditory Verbal Learning Test (AVLT) and the California Verbal Learning Test (CVLT).[84,183,185–187] These aforementioned multitrial tasks provide an opportunity to assess various aspects of working memory processes involving frontal lobe function in addition to learning. Studies incorporating the CVLT and AVLT indicate that decreased performance can also be due to inefficiency in guiding the retrieval process,[188] especially if the right frontal areas are damaged.[189,190]

Difficulty in transferring information from working memory to long-term memory, i.e., consolidation, can be disrupted by the appearance of distracting or interfering material[191] as well as failures to appropriately organize information. Patients suffering from TBI seem to be most vulnerable to the debilitating effects of interference possibly due to insult to the frontal lobes, especially the left frontal[189] or the medial temporal lobe areas. Studies following TBI suggest that immediate recall (measured by span tasks) appears to be largely intact.[192,193] However, when interference is imposed, memory performance is significantly affected indicative of difficulties in consolidating declarative information into long-term memory.[188,192] Interference can be introduced in the form of a delay or in the form of a competing stimulus.[193] Even a 10-second delay between stimulus presentation and response has been reported to affect recall performance.[194]

The current view of the organization of memory and its processes has been developed in part as a result of focal lesions both in human and in animals and their resulting effects on various memory tasks. TBI, however, rarely causes circumscribed lesions. Subsequently, multiple memory systems may be affected.[121,186,195]

Research suggests that patients with moderate-to-severe CHI are able to learn new information, but at a decreased rate compared to normal subjects. Furthermore, the ability to recognize information is superior to their free recall skills.[185,188,196] Although, as a group, CHI subjects tend to have a more passive learning style, subgroups of patients that apply active memory strategies have been reported. These patients typically have better working memories in comparison to patient subgroups that do not use active memory strategies. Patients with moderate-to-severe TBI benefit from pictorial presentation of verbal material rather than auditory presentation of information.[185,197] Pictorial superiority is evident, not only in patients with TBI, but also with other pediatric and adult patient groups as well as in healthy controls.[198–200] The observed visual effect may be attributed to the way the brain process visual versus auditory materials. For visual processing of pictures, bilateral visual networks are engaged from the level of the retina all the way to the visual association areas (bilaterally via the brain stem, thalamus, and primary visual strips). In contrast, auditory information is processed bilaterally for about 100 ms. Signal arriving into the right hemisphere will cross over to the left hemisphere for verbal working memory tasks. The presence of these two temporally distinct sensory pathways have been confirmed in an EEG study using single trial analysis with healthy young controls examining the neuronal correlates of the behaviorally observed stimulus modality phenomena.[201] Therefore, the bilateral processing of pictorial material enhances working memory performance by reducing demands on allocation of resources.

The use of visual imagery as a remedial approach to facilitate verbal recall seems to be effective for patients with mild memory impairment in TBI.[202] However, elaborate visual imagery techniques are not effective after TBI due to increased mental effort demands.[179,203–205] Furthermore, patients with severe memory impairments benefit more from external memory aids and alerting devices for activities of daily living, provided that they receive extensive training for the use of the strategy or device.[107,206] Specific external memory strategies, such as the implementation of a memory notebook, may be beneficial for everyday (or prospective) memory functions, such as remembering important dates and appointments.[207,208]

Teaching domain-specific memory tasks as they pertain to a given job may be successful because they incorporate procedural memory, repetition, and routine building.[208–210]

However, the application of that knowledge to novel situations and problems requires declarative knowledge of strategies as well as intact executive abilities,[15,107] frequently impaired after moderate-to-severe TBI. The hierarchical perceptual tasks proposed later on in this chapter are designed to facilitate working memory and executive abilities.

VERBAL LANGUAGE

The verbal–logical language system collectively is another important system that is related to higher cognitive function. For instance, strategies for successful encoding and retrieval of information and categorization techniques typically incorporate verbal language. Consequently, language is used routinely during neuropsychological testing for the assessment of cognitive abilities, such as working memory, semantic knowledge, verbal reasoning, and problem solving.

TBI can affect language directly and indirectly. Direct focal damage to the language-dominant regions of the left hemisphere and disruption of language-specific networks can result in aphasic symptomatology. The patient may have difficulty processing linguistic types of information and experience decline with receptive and expressive language.

More often though, TBI is not associated with traditional aphasic syndromes. Although aphasia may be present during the early stages of the recovery process due to direct lesions in language-specific networks of the left hemisphere, the clinical picture usually evolves, and the primary language deficits center in the area of word finding, lexical retrieval, and verbal fluency. These can persist for at least a year postinjury.[211,212]

The neuropathology of TBI as described earlier in the chapter involves multifocal lesions. Recent evidence in the past two decades indicates that multiple cortical and subcortical brain regions (in both hemispheres) are activated during language tasks even though the left hemisphere demonstrates greater activation.[213] Hence, focal damage to cortical and subcortical brain structures in either hemisphere, such as the medial temporal lobes, the frontal and parietal lobes, the thalamus, and the fusiform gurus, may result in the disruption of various cognitive processes that support language (i.e., working memory and organization) and language-specific networks. Furthermore, DAI can result in generalized cognitive disruption that often affects complex linguistic abilities.

Difficulties in discourse organization and other extralinguistic difficulties are often a result of cognitive nonlinguistic processes that support language. Damage, dysfunction, or disorganization of attention, memory, categorization, and executive control (including self-awareness and self-inhibition) can hamper language abilities during discourse. These difficulties can be manifested as problems in social communication.

Common deficits in social communication or pragmatics (i.e., social use of language which is context-dependent) can be observed during discourse. For example, the survivor of TBI may have difficulty in conversational turn-taking, which may be manifested as lack of verbal sensitivity or as verbal impulsivity. Reduction in cognitive and linguistic abstraction will interfere with verbal reasoning and sometimes in using and interpreting humor as well as in difficulty interpreting nonverbal language cues or ambiguous statements. Furthermore, attention and memory problems may pose challenges in remembering names and events and in processing large amounts of material during discourse. These difficulties may result in "out of sync" statements contributing to social awkwardness.

Consequently, deficits in language use and language perception or interpretation can create significant social and communication burden for the patient with TBI. Linguistic communication therapy in TBI focuses on discourse management skills (during individual and group therapy formats) and in treating the underlying cognitive deficits that contribute to the linguistic communication impairment. The categorization program described later in this chapter is an example of such an approach that begins with basic object description and progresses hierarchically into linguistic abstraction. For more information on the major brain areas involved in language functions, language networks and their processing characteristics, and the effects of brain lesions on language functions, the reader is referred to Coppens and Papathanasiou,[214] Benson and Ardila,[215] and Hillis.[213] Finally, taking into consideration the intimate relationship between language abilities, educational level, culture, and socioeconomic status, rehabilitation of language abilities should take into consideration the patient's native language, dialect literacy, and premorbid language demands. Furthermore, staff should recognize that levels of communication competence and communication characteristics may vary as a function of communication partner, environment, communication demands, communication priorities, fatigue, and other personal factors.[216]

CATEGORIZATION

In the hierarchy of cognitive function, complex or "higher" reasoning activities, such as categorization (including object recognition and perception/action), problem solving, and decision-making, are those that require the coordination of several of the basic systems. Because of the greater complexity inherent in these higher-level tasks, understanding the alternative processing strategies and subsystems deployed by the executive system becomes important for modeling individual performance. When we categorize, we assign objects or events into groups. This may be done to support other types of activities or decisions that have to be made—that is, categorization itself is a process that serves as a subcomponent to other higher processes. For example, expert problem-solvers must categorize the situation as a particular kind of problem before solutions are made available. The research on categorization distinguishes between aspects of classifying and recognizing everyday objects and situations and the learning of novel categories. These two processes can be dissociated in brain-damaged individuals[217] in that, sometimes, one can lose the ability to learn new categories

(e.g., in Parkinson's disease), but not lose old familiar categories. The opposite pattern has been observed as well with some deficits leading to the loss of specific highly learned categories[218,219] with no obvious general category-learning problems. An attempt to integrate these two distinct areas of research suggests that our knowledge of natural categories and common objects is likely to have been acquired through the use of a similarity-based system.[220,221]

Recognition and categorization of everyday objects

The visual recognition and categorization of everyday objects involve two anatomically and functionally distinct pathways specialized for different kinds of information. As seen in Figure 28.1, the ventral pathway (through the temporal lobes) subserves passive recognition in which the object is perceived as a kind of thing that the observer has seen before. This recognition includes all aspects of visual memory, such as form, function, the object's typical location, and many other associated memories. The dorsal pathway through the parietal lobes mediates visually-guided behavior, such as reaching and grasping of objects and self-locomotion (Figure 28.1). The dorsal perception-and-action system is understood in terms of spatial attention, orienting, and motor control[147], and overlaps significantly with the orienting networks described above.

Deficits in the passive object recognition system due to brain injury led to dissociations in categorization ability as a function of the type of stimulus material. Most often, patients lose the ability to recognize living or animate objects while artifactual recognition is spared although the opposite dissociation has been observed. This pattern of results fueled a long-running debate regarding how the semantic (memory) system is organized.[222] One view held that concepts are represented along domain-specific modules that have evolutionary significance, specifically the categories of plants, animals, tools, and conspecifics.[223–225] A second perspective argued in favor of a sensory-motor distributed model in which concept knowledge was organized in terms of perceptual and function features.[226] Recent views of the concept system based on object naming tasks suggest that both aspects of representation may be correct.[223,227,228] In their tripartite model of concept and lexical access, Damasio and colleagues argue that concept representations are separable from the word form systems that reside in classical language areas. Mediating between the two in the left inferotemporal area is a neural structure that links the concept knowledge system to the word form system. They have provided evidence that this intermediary system is modality-neutral, open to access through any sensory channel,[228] but is categorically organized in the manner suggested by Caramazza and his colleagues.[225,229–231]

As stated previously, a more recent model of semantic memory incorporates a domain-general hub located in both the right and left temporal lobes, termed the "semantic hub,"[148] linking object properties and conceptual understanding in a modality-free structure to support generalization across concepts. There is clear evidence in vision of a hierarchical recognition process that begins with early feature processing (such as orientation, motion, and color) and leads to the processing and representation of objects and object classes in the inferotemporal cortex.[232] We propose that cognitive treatment should incorporate a systematic hierarchical protocol beginning with early feature identification in order to retrain the passive object recognition system. The tasks should consist of both animate and inanimate classes of objects in order to account for the possibility of domain specificity in the representation of visual memories.

Recognition and categorization of novel situations

When people are faced with having to learn to categorize novel objects or situations, current cognitive theory suggests

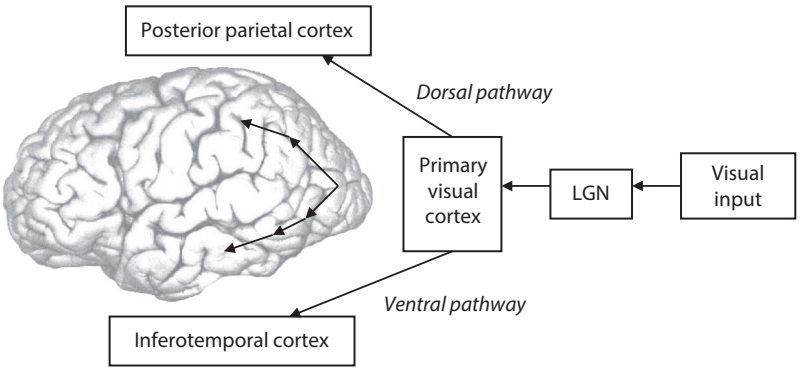

Figure 28.1 Pathways for recognition and categorization of everyday objects. Input from the retina traverses two major visual pathways in the primate brain. Information supporting visually-guided action (e.g., reaching) is routed through the lateral geniculate nucleus (LGN), the primary visual cortex in the occipital lobe, and on to the posterior parietal regions (the dorsal pathway). Visual attributes that are necessary for the identification and recognition of an object and its related properties are processed in the ventral pathway, including the LGN and the primary visual cortex, ending in the inferotemporal cortex.

they may be able to recruit one of several specialized systems for this purpose.[217,233] Two of these are "explicit" in the sense that their processes and outputs are consciously available to the category learner. The most important of these, the rule-based or rule-governed category system, involves the use of explicit verbalizable rules and hypothesis testing to determine category membership and, hence, relies heavily on EF for its operation. The other explicit system requires significant episodic memory in that categorization is accomplished by the recall of previously experienced category members, or exemplars, that are similar to the present novel object.[234] Exemplar-based categorization likely draws upon brain structures known to underlie episodic memory performance—that is, the medial temporal lobe including the hippocampus. This type of process would be efficient only for categories of a few members or if the mapping from examples to category is unstructured (ad hoc). Once the number of category members exceeds the limits of working memory, other more robust procedures are brought to bear.[235]

It has been observed that even in the case of severe deficits in episodic memory and/or in the case of nonverbalizable category rules, individuals can still learn to classify objects.[235,236] An example of the latter kind of category learning problem is the complex pattern recognition required in such cases as radiology or sonography in which the category boundaries are quite fuzzy and the elements in the pattern combine in nonlinear or interactive ways to specify identity. Learning in such cases relies on the procedural learning system described in the earlier section on memory.[217,237] Learning in this system requires immediate feedback on the correctness of the classification response due to its reliance on dopaminergic pathways.[238] This contrasts with learning in the rule-governed working memory system in which feedback can be delayed or absent and learning can still occur. Finally, some types of nondeclarative category learning recruit the perceptual representation system that underlies priming. For example, in a task described as prototype distortion learning, category examples are generated by the statistical perturbation of a prototype pattern. The learner's task is to discover which patterns were generated by the prototype and which were not, deemed an "A or not A" task to distinguish this from the more traditional "A or B" category learning task. The prototype is untested during learning, but strongly endorsed as a member of the category during a transfer test. Neuropsychological studies show that individuals with compromised medial temporal lobe systems and basal ganglia disease (e.g., Parkinson's patients) show normal functioning on the "A, not A" version of this task.[239,240] A recent study demonstrated that prototype learning of the "A, not A" type can be dissociated from the category learning version under the hypothesis that learning in the former version leverages the perceptual representation system, whereas the latter version recruits medial temporal lobe structures.[241] Neuroimaging results also show learning-related changes in the visual cortex that support visual priming and similar types of perceptual learning.[242]

Which system is recruited for a particular problem is a complex interaction of task characteristics, individual differences, and stage of learning.[142,243] Evidence suggests that if the declarative (rule-based) strategy is effective early on, it will inhibit the emergence of a procedural strategy, even if the latter becomes necessary later in learning.[244] This suggests that understanding the relationship between individual neuropsychological characteristics, such as EF or other reasoning type processes, and performance in categorization retraining tasks may be important in the design of cognitive retraining tasks.[14]

Moderate-to-severe TBI seems to interfere with the patients' ability to use attributes to describe objects. In a study by Constantinidou and Kreimer,[245] subjects with moderate-to-severe brain injury provided significantly fewer attributes to describe common household objects compared to matched noninjured subjects. Subjects with brain injury were able to learn a list of eight core attributes, such as color, shape, composition, and weight. Finally, they were able to apply these attributes to describe another set of common objects more effectively compared to their spontaneous description. However, their performance was, at all times, significantly poorer than that of noninjured subjects. These findings support the need for a systematic rehabilitation program to improve the categorization abilities of patients with moderate-to-severe TBI. We discuss such a program in the section on Directions for rehabilitation.

EXECUTIVE FUNCTIONING

Current theoretical frameworks of EF propose a multidimensional construct. Although executive control is an important component of attention and memory processes, EF is considered to be a group of higher-order integrative processes by which people monitor, manage, and regulate the orderly "execution" of goal-directed ADLs (i.e., activities of daily living).[206]

Neuroanatomical correlates of EF

The literature offers multiple theoretical models of EF. The perspectives adopted by the various EF models depend, to a great extent, on their respective theoretical framework.[246] From an anatomical perspective, the frontal lobe area is, most often, associated with EF; in fact, impairment in EF at the more severe level is sometimes referred to as "frontal lobe syndrome." However, as pointed out in the previous sections, lesions in the frontal lobes can affect other areas of cognition, such as attention, memory, and language. Furthermore, tasks purported to measure EF are not exclusive to the frontal lobes and are typically not uniformly sensitive or specific to frontal lesions.[248] Therefore, it seems more appropriate to frame the neuroanatomy of EF from a frontal–subcortical network (FSC) perspective rather than a strict localization approach.

Saint-Cyr, Bronstein, and Cummings identified five FSCs most relevant to EF.[247] The circuits are arranged in a parallel pattern and typically begin from the cortex and connect down through subcortical structures (striatum and globus pallidus of the basal ganglia) until reaching the thalamus and then returning to the cortex. Two of the five circuits are primarily

motor (e.g., motor, oculomotor). The remaining three are most important to cognitive and behavioral processes: the DLPFC, orbitofrontal circuit (medial and lateral), and the anterior cingulate circuit. This organization of cortico–striato–thalamo–cortical circuits explains why lesions in subcortical areas, such as the basal ganglia (which are closely linked to the cortex through the aforementioned networks), can result in much the same pattern of behavior dysfunction as would be seen from a lesion affecting the cortical areas of the frontal lobes.[246]

> The orbitofrontal circuit has two parallel subcircuits (i.e. lateral and medial). The hallmark of dysfunction in the circuit is personality change. Notable difficulties include irritability, emotional ability, inappropriate responses to social cues, lack of empathy, as well as acquired obsessive-compulsive disorder. …Individuals with damage to the circuit can often perform normally on EF measures. The anterior cingulate circuit generally mediates motivated behaviour and damage typically resulting in an apathetic syndrome. Bilateral lesions may result in akinetic mutism. Symptoms of dysfunction to the anterior cingulate circuit include poverty of spontaneous speech, poor response inhibition, reduced creative thought, and indifference to pain. The dorsolateral prefrontal circuit is the one most closely associated with executive functioning. Damage to the circuit may result in poor organizational strategies, poor memory search strategies, impaired set shifting in maintenance, as well as stimulus bound behaviour and environmental dependency.[245]

EF domains

The Joint Committee on Interprofessional Relations between the American Speech-Language-Hearing Association (ASHA) and Division 40 (clinical neuropsychology) of the American Psychological Association (APA) provide an integrative framework for the assessment and treatment of EF in survivors of TBI. The Committee proposes three primary EF domains: 1) planning and initiation, 2) maintenance and flexibility, and 3) regulation and effective performance.[246]

Domain 1, planning and initiation, incorporates task setting and goal formulation of activities in order to achieve goals and objectives in addition to initiation of goal-oriented behavior, allocation of attentional resources, impulse control of inappropriate behaviors, and termination of activity through ongoing monitoring.

Domain 2, maintenance and flexibility, refers to the individual's ability to maintain behavior in order to complete an activity or solve a problem. Inherent to this domain is the ability to approach problems from a different direction, to understanding perspectives other than our own, and to modify one's behavior based on feedback.

Finally, Domain 3, regulation and effective performance, incorporates self-regulatory mechanisms and self-awareness of strengths and weaknesses and the ability to understand the impact of one's actions on others. In order for purposeful activity to culminate in effective performance, one needs to self-regulate emotions and behavior and to implement continuous monitoring based on internal and external feedback.

Evidence-based reviews of clinical studies investigating effective strategies to manage EF deficits suggest the use of metacognitive strategies to increase awareness and self-regulation in patients with TBI.[107,249] These strategies could be used in conjunction with efforts to develop strategies in order to manage other cognitive deficits, such as attention, memory, and language–communication disorders. Furthermore, the use of formal problem-solving strategies as they relate to daily life is recommended for patients with TBI.[107,250]

DIRECTIONS FOR REHABILITATION

The cognitive system is comprised of hierarchical processes and systems. Depending on specific task demands, different levels of processes are recruited for successful task completion. At infancy, the individual begins with basic concrete abilities, such as directing attention to a given object or person. Infants and young children learn features of objects (such as color, texture, and shape) in a predictable manner. These skills enhance their ability to learn categories, discriminate, and make generalizations.[251,252] As the cognitive system matures, attention capabilities become more sophisticated. Cognitively intact adults are able to direct attention, discriminate, shift, and sustain response sets in the presence of distraction. Brain injury causes a disruption of neuronal systems and interferes with the efficiency of the cognitive hierarchies. Consequently, postacute cognitive rehabilitation (CR) should implement systematic hierarchical treatment protocols that target attentional, memory, categorization, and abstract thinking tasks to restore impaired cognitive processes.[253–255] A systematic hierarchical approach has been suggested in the brain injury rehabilitation literature as a means to rehabilitate and reorganize cognitive systems and restore concept formation and cognitive function.[256–258]

Where should CR begin? One needs to consider that even the most minimal cognitive act from input to output involves recognition and categorization. In the previous editions of this book, we proposed that postacute CR should implement a hierarchical program beginning with basic levels of categorization, such as feature identification, with the ultimate goal to target higher processes, such as abstract thought, decision making, and problem solving. We developed a treatment model that integrated principles of cognitive theory and models of category learning,[259,260] language theory,[251,252] and rehabilitation[253,261] for the design of hierarchical tasks to treat the two aspects of categorization described above: 1) recognition and categorization of everyday objects and 2) recognition and categorization of novel situations. The theoretical model was the basis for the categorization program (CP).[14,254,262]

As seen in Appendix 28-A, the first part of the CP begins with a very basic level of concept formation and thought productivity, which includes asking and training the person to express as many attributes as possible about a common object. The person progresses through the various levels of the CP as he or she achieves criterion at each level. Each level becomes increasingly demanding, requiring more cognitive effort. The stimuli begin with concrete objects (in order to minimize cognitive distance) and progress gradually to abstract ideas. Abstract reasoning, mental flexibility, and problem solving abilities are the targets of the higher levels of this systematic perceptual training program.[262,263]

The CP integrated principles of cognitive neuroscience and rehabilitation and designed hierarchical tasks for the similarity-based and the rule-governed systems described previously. The tasks begin with basic feature identification and feature extraction (such as color, shape, and size) and progress to higher levels of concept formation and abstraction (such as rule-based decision making). The CP is a systematic hierarchical training program consisting of eight levels. It provides a standardized approach to categorization training, yet, it incorporates mastery criteria for each level in order to account for individual differences. Furthermore, it implements systematic cueing hierarchies and errorless learning to facilitate patient training and learning. A preliminary study with the CP[254] and a follow up RCT[14] indicate that the CP is effective in improving categorization abilities in patients with TBI who are enrolled in postacute rehabilitation. Patients who were treated with the CP demonstrated greater gains on neuropsychological tests than those patients who received the standard treatment. Furthermore, the CP facilitated the generalizability of skills into new tasks that required the application of high-level categorization abilities, including mental flexibility. Research in patients with TBI who received this protocol during their postacute rehabilitation phase indicates that the CP helps patients improve their cognitive performance during neuropsychological tests, categorization tasks, and functional outcome measures.[14,254]

In summary, the remedial systematic hierarchical approaches are based on the fact that our cognitive system is comprised of systematic hierarchical components. All of these basic and complex systems tie together in order for the individual to learn and adapt to the environment. The combination of hierarchical remedial (or restorative) therapy that follows a neurodevelopmental approach along with compensatory techniques could be used together in order to maximize the patient's level of functioning during the rehabilitation process.

EFFICACY RESEARCH

Efficacy research in the area of CR has a history of about two decades. The proliferation of TBI outcomes research in the past decade is consistent with the 1998 consensus statement on TBI, which calls for new and innovative research in the area of CR.[264] Yet, efficacy research in TBI CR causes a multitude of methodological and ethical problems. Behavioral researchers are called to aspire to the "gold standard," the double-blind randomized controlled trial, implemented in pharmacological research. Although this type of elegant research protocol might work in a behavioral neuroscience laboratory, it is certainly not pragmatic for the daily life of the rehabilitation team that is subjected to patient health problems that interfere with treatment, insurance funding cuts, staff turnover, and scheduling conflicts. Yet, it is important that efficacy research demonstrates that the treatment is both effective and efficacious—that is, treatment ought to cause a positive change to the targeted dependent variable in the setting that is designed to be implemented. Consequently, outcomes research that takes place in the actual clinical setting should be designed carefully in order to maximize experimental control and account for potential sources of variability that might compromise its results.

CR is an integral component of most TBI rehabilitation centers. Yet, there is great variability in the treatment methodology implemented at the various centers across the United States and internationally. Groups such as the Brain Injury Interdisciplinary Special Interest Group of the American Congress of Rehabilitation Medicine (BI-ISIG),[107,206] the special task force of the European Federation of Neurological Societies,[265,266] and the Academy of Neurologic Communication Disorders in the United States[267] have conducted extensive reviews of the literature in order to assess the evidence on CR and develop clinical practice guidelines.

As Malec[15] pointed out, scientific inquiry has a sequence of development and is a "slow process that frequently begins with uncontrolled naturalistic observations leading to single-case and other limited experiments that in the long-term provide a basis for more sophisticated experimental designs" (p. 232).[15] The majority of CR research continues to be classified as Class III evidence (i.e., single subject with quantitative analyses and clinical series without concurrent controls). The BI-ISIG has published three systematic reviews in the past 15 years evaluating a total of 370 interventions. The latest BI-ISIG review examined research articles published between 2003 and 2008, and 112 out of the 149 studies reviewed were retained in the analysis.[107] It included 19 Class I and Ia (prospective RCTs), 11 Class II (prospective, nonrandomized cohort studies or multiple baseline or retrospective, nonrandomized case-control studies) and 82 Class III studies. The prior review included studies between 1998 and 2002 and yielded classified 17 Class I, eight Class II, and 62 Class III studies.[206] In contrast, the first BI-ISIG review[268] included *all* peer-reviewed published studies on CR prior to 1997 and identified 39 studies as Class I studies. Therefore, the publication of an additional 36 new Class I studies in the 11 years since the first published review and the increased interest in efficacy studies (over 144 studies in the past decade) is an indication of the development of CR research in brain injury.

Cicerone et al.[107,206] proposed that research should focus on standardized interventions (which we believe need to be based on theoretical models of human cognition and learning) and the identification of various components of complex interventions (i.e., active ingredients). Research protocols need to use sensitive measures to measure changes that directly relate to the hypothesis at hand and to the changes (or behaviors) that the study intends to measure. Furthermore, both functional measures and formal neuropsychological measures that are not only sensitive, but also have been validated with the TBI population, need to be incorporated to measure changes as a result of specific treatment.

The most dramatic recovery following brain injury occurs during the first year postinjury, also known as the spontaneous recovery stage. Efficacy research may want to identify treatment strategies that enhance recovery during the first year postinjury. It is possible that certain treatment paradigms may yield different results depending on the time since injury.

In addition to chronicity, injury severity is another factor that needs to be investigated in relationship to rehabilitation outcomes. The length of impaired consciousness, the length of posttraumatic amnesia, and the Glasgow Coma Scale scores have been traditionally used to determine injury severity. In the recent years, the presence of genetic markers, such as the Apolipoprotein E4 allele and elevated serum 100B protein, have also been associated with poorer recovery.[268] Efficacy research may want to investigate whether certain treatment paradigms are more beneficial for patients with specific neuropsychological and biophysical profiles (i.e., is technique A better than technique B in treating this population with X characteristics?) in order to design treatment paradigms that target patient needs more effectively. Finally, other patient characteristics and variables, such as the notion of cognitive and brain reserve, may influence outcomes.

Relating to CR is the patient's ability to apply strategies that guide learning and retrieval of information. According to the CR hypothesis, individuals with higher reserve are able to cope with brain pathology through some form of active compensatory strategy better than those with lower reserve. Thus, greater CR could allow individuals to cope better with the cognitive changes associated with aging or brain injury by promoting more flexible usage of cognitive processes and implementation of new strategies.[52,270] CR is not a unitary theoretical construct, and variables such as education, social and cognitive engagement, vocabulary knowledge, and reading abilities have been incorporated in latent model analyses in order to define it and determine its prognostic utility in rehabilitation.[55,56] Giogkaraki et al.[55] reported that higher levels of CR have a moderating role in reducing the direct negative effect of age on verbal episodic memory and on EF in healthy aging. Consequently, in addition to injury or disease specific characteristics, CR could be another parameter for consideration during patient rehabilitation.

CONCLUSIONS

Children learn new skills by attending, discriminating, categorizing, and acting upon their environment. The essence of CR following brain injury is to teach the patient new skills, remediate old skills, refine existing abilities, and teach compensatory strategies in an integrative manner to enhance and maximize the patient's level of functioning. Evidence presented in this paper from cognitive theory, neurobiology, psychology, and clinical research support the use of remedial techniques using systematic hierarchical programs targeting basic and complex cognitive systems. Evidence indicates that in postacute brain injury rehabilitation, CR goals addressing attentional, language, categorization, visual processing, problem solving, and abstract skills may have lasting effects in patients with CHI.[107,206,255] The categorization tasks included in the appendices are being used as examples of how a hierarchical treatment model of a standardized therapy modality might be developed.

Neurobiological research on learning suggests that repetition enhances learning. We could assert that systematic, hierarchical restorative training as part of a CR program could facilitate adaptive neuronal sprouting occurring during the spontaneous recovery process. Furthermore, CR would provide environmental support and stimulation that will facilitate central nervous system functional reorganization as part of the recovery process. As neuroimaging techniques improve, future research may provide clear information on the extent of neuronal reorganization and CR after TBI.

Successful rehabilitation following brain injury is a complex process. The focus of this chapter was to apply cognitive theory and neurophysiological principles of learning and recovery as they relate to the restoration of attention, memory, and categorization skills following TBI. However, CR is part of the large umbrella of neuropsychological rehabilitation. As part of that, the person's psychosocial functioning, self-awareness, self-acceptance, emotional and environmental support mechanisms, and access to the community and services are necessary components for successful rehabilitation. When all of these processes function in synergy, the outcome is greater than the sum of its parts, resulting in an optimal treatment outcome.

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APPENDIX 28-A

The categorization program[261] is comprised of two parts and eight levels, which are designed to retrain a series of categorization abilities. Each level in both parts builds on the skill set trained and applied in the previous level; therefore, a range of concrete-to-abstract thinking abilities is targeted. The purpose, specific aspect of categorization trained, and the ultimate goal of each level are outlined below.

Part A

LEVEL 1: PERCEPTUAL FEATURE IDENTIFICATION AND APPLICATION

The purpose of this section is to train perceptual feature identification, thereby building a framework for cognitive structures. The retraining of basic categorization abilities will build the foundation for more abstract functions and will facilitate communication during word-finding difficulties. The goal is to have the patient learn eight perceptual features and consistently apply all the features to describe common objects. Objects are presented via a range of stimulus types, including real objects, color photos, line drawings, written words, and spoken words.

LEVEL 2: SIMILARITIES AND DIFFERENCES

The purpose of this level is to apply the eight perceptual features trained in Level 1 to compare objects. Identification of similarities and differences between two objects of the same and of different categories using the eight perceptual features is utilized in order to train conceptual thinking. The process of applying the trained perceptual features is the next layer of the continuum of concrete-to-abstract functional abilities. Stimulus types include color photos, written words, and spoken words.

LEVEL 3: FUNCTIONAL CATEGORIZATION

The purpose of this task is to identify functional categories and maintain the delineations within that category. There are two specific foci in this level that require the consideration of the features of the objects trained and applied in Levels 1 and 2: The application of retrieval strategies to generate novel items that belong in a given category and the mental flexibility required to generate alternate uses for the objects in a given category. This task enhances functional problem-solving abilities and mental flexibility.

LEVEL 4: ANALOGIES

The purpose of this level is to apply both the categorization abilities trained in Levels 1–3 and inductive reasoning skills in order to identify and match the concepts represented in analogies. The analogies progress from concrete to abstract in order to train word abstraction. Stimulus materials include multiple-choice responses for each analogy that will aid in the training process of word abstraction as needed.

LEVEL 5: ABSTRACT WORD CATEGORIZATION

The purpose of this level is to further develop concept formation and abstract conceptual thinking. The goal is to identify similarities and differences in abstract verbal concepts. The generation of similar word pairs using synonyms that represent the relationship between the words is incorporated to enhance cognitive and linguistic flexibility.

Part B

The exercises in Part B are constructed to examine and train learning rule-based classification strategies. A core set of five conditions or rules is utilized in Levels 6–8. The conditions, which stem from cognitive psychology, are affirmative, conjunctive, disjunctive, exclusive, and conditional. The stimuli for Part B range from concrete to abstract and include shapes (Level 1), gauges (Level 2), and written word groups (Level 3). The goal of Part B is the formulation of the rule that governs the classification of each stimulus into either Category A or B. Errorless learning is implemented as a cueing technique to counter frustration and aid rule formulation. Ultimately, the tasks in the part will enhance decision-making and problem-solving abilities.

LEVEL 1: PROGRESSIVE RULE LEARNING 1

The stimuli for Level 6 vary along two dimensions: shape and color. The nine stimuli include squares, circles, and triangles that are red, white, and black. Each stimulus is presented individually, and a formulation of the rule that classifies each stimulus into either Category A or Category B follows.

LEVEL 2: PROGRESSIVE RULE LEARNING 2

The stimulus presentation for Level 7 of Part B is gauges that include two dials that must be interpreted as a single unit. This level forces generalization into a real-world situation by simulating the reading of gauges at a power plant. The determination of operational or not operational for each stimulus is utilized, and the cumulative interpretation of each judgment leads to the formulation of the rule that classifies the stimuli for each of the five conditions.

LEVEL 3: PROGRESSIVE RULE LEARNING 3

The final explicit rule task contains the same underlying structure as the earlier two levels; however, this time a judgment is made using stimuli constructed from dimensions of language. This further abstracts the rule formulation, and forces generalization of training to a real-world situation. The stimuli in this task consist of a summary of three laboratory tests (lung capacity, heart fluid, bone marrow count) and their orthogonal combination with two measurement adjectives (low, high).

CP-related dependent measures

The three CP tests assess the effectiveness of the CP program and compare performance before and after the training. CP Test 1 relates to Part A and CP Tests 2 and 3 to Part B treatment activities. In addition, the program implements four probe tasks. These were designed to assess the ability to generalize information learned on the CP to other tasks not directly related to the CP training tasks. They are administered at four different times during the training. The first probe task is administered at baseline, the second after Level 2 (Part A), the third after Level 5 (Part A) and the last one after completion of the entire program at post-testing.

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Management of residual physical deficits

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INTRODUCTION

In the early 1900s, John Hughlings Jackson, considered to be the father of British neurology, opined, "You can't treat a hole in the head." There was no science at the time to say otherwise. No one was thinking "neurorehabilitation" at the dawn of the twentieth century. However, as we look back from the twenty-first century, we see 100 years of phenomenal progress throughout the broad spectrum of scientific knowledge. This is especially true of the science of neurology and its grand master, the brain. It was that progress that took us from Jackson's undisputed edict in 1900 to "treating a hole in the head" in reality with amazing success by 2000.

We thank the pioneers of early neurology and rehabilitation who questioned the status quo and moved with the "science of their time" to forge many new paths. For today's neurologic physical therapist (PT) and occupational therapist (OT), it began with such innovators as Bobath,[1–3] Rood,[4] Knott and Voss,[5] Brunnstrom,[6,7] and Ayres.[8] As neuroscience evolved through the decades, it uncovered deep and secret things. With each revelation, you could hear an "aha!" followed by the sound of tinkering as the researcher made adjustments to turn a treatment technique toward greater effectiveness. Then, as now, the early innovators did not give up and stagnate; they evolved. The Bobath concept[1] of today is a good example of this process.

Neurologic PTs and OTs of the twenty-first century continue to receive instructive guidance from many talented contemporaries who keep the fires of research and development burning. Among them are respected researchers, teachers, and authors, such as Faye Horak, PhD, PT[9]; Darcy Umphred, PhD, PT[10]; Anne Shumway-Cook, PhD, PT[11]; and Marjorie Woolacott, PhD.[12] In addition, neuroimaging technology has opened windows to allow us to watch the brain at work. Now we have evidence of cortical reorganization

and neuroplasticity that is validating the effectiveness of good neurorehabilitation treatment techniques.[13]

As a result, the hunger for evidence-based treatments is driving the engines of research. The Sections on Research and Neurology of the American Physical Therapy Association (APTA) are developing projects to assist therapists in identifying the most effective treatments through use of reliable, validated tests and measures. The Evaluation Database to Guide Effectiveness (EDGE) task force provides an online database that continues to review and add information each year (http://www.rehabmeasures.org, link: Instruments).

EVALUATIVE PROCESS

The purpose of a complete evaluation is to identify both obvious and subtle deficits in order to set the stage for an effective continuum of treatment and achievement of realistic goals. Although it may appear that specific areas of evaluation and treatment have been designated to the PT or the OT, there is no intent to imply that these designations are, necessarily, as described. The important point is that every area must be appropriately evaluated and aggressively treated by the best therapist for the task.

It is not uncommon in the TBI population to encounter persons with seemingly more advanced skills than are actually present. A good example can be found in the person who is able to ambulate reasonably well when certain challenges are not present although, when balance is challenged, delayed protective reactions may be revealed. A good therapist not only assures a thorough evaluation, but is also an astute observer of the little things lurking in the shadows that could trip the patient.

In an efficient admission to the TBI rehab program, the therapeutic team will be informed in advance about the patient's injury and medical and early rehabilitation histories and will be given a glimpse into the preinjury history and lifestyle prior to the commencement of the individual's therapy. Recommendations, pertinent factors to explore, and discussion of possible discharge options should be reviewed prior to admission. The collection and presentation of this information should be provided by experienced field evaluators (see Chapter 22 in this text by Ashley on field evaluation).

All therapists should be able to recognize the influence of various cognitive deficits that impact the patient's ability to problem solve, organize, and sequence motor acts. The rehabilitation team needs to understand impairments in perception and integration of the senses influencing movement, balance, and position in space.

Agitation or other inappropriate behaviors can seriously hinder progress. Therefore, proper staff training and effective approaches to behavior management should be expected in a comprehensive TBI program (see the chapter in this volume on applied behavior analysis). Behavioral deficits are a fairly common sequelae in TBI. Many individuals are tactilely defensive and/or easily overstimulated by even modest amounts of stimuli. Disorientation adds to the likelihood that verbal or physical aggression or withdrawal from treatment will occur. The proximity of physical and occupational therapy treatments together with the factors listed earlier make it quite likely that therapists in physical rehabilitation will require skills in behavioral intervention.

Behavioral programming should be superimposed on treatment in either physical or occupational therapy. Application of defined behavioral strategies and programs can be best achieved in tandem with physical rehabilitation programming. Occasionally, it will be necessary for behavioral programming to supplant other programming; however, careful monitoring should be conducted to ensure that rehabilitation programming is undertaken as soon as possible. It is neither realistic nor necessary for behavioral issues to be completely resolved prior to initiation or continuation of rehabilitation programming. In fact, there are very few instances in which rehabilitation programming should be deemed "nonfeasible" due to behavioral deficits.

Emotional problems may manifest in problems with cooperation or motivation. It is hoped that a team member is available to assist in addressing of such problems; however, the PT or OT may become the de facto counselor to the brain-injured person. Often, the intimacy of the physical rehabilitation treatment setting allows the breakdown of psychological defense mechanisms or allows the development of levels of trust and understanding that enable access to the person's emotional status. Overall, discussion among team members will allow all aspects of the clinical presentation to be shared and treatment approaches to be developed by the appropriate discipline.

As the individual enters the initial PT and OT evaluation sessions, the therapist should explore him or her as a whole. There should be no assumptions made about functional skills despite the report of previous diagnoses, treatment records, or initial appearances. Such premature assumptions can lead to inappropriate or absent treatment.[14]

Evaluation should be performed in a variety of clinical, residential, and community settings. Although personal lifestyle and medical histories were introduced in the preadmission information, the initial session should still allow time for getting acquainted. During this interaction, trust and understanding should be nurtured. To signify respect, the therapist should attempt to explain the purpose of each test or exercise and relate it to tasks in daily life. Most patients will respond to this type of interaction and will probably attempt to rise to a realistic level of expectation. A vital aspect of the therapist's role is that of motivator.

The evaluation should be thorough and well documented in quantitative and qualitative terms. Utilization of videotape is an excellent tool to assist in recording the person's performance progress from evaluation throughout treatment to discharge. If the person is unable to follow directions or is uncooperative, document observations of how the individual functions. For example, in an evaluation of a person who was heavily medicated, depressed, and unable to respond to usual evaluative techniques, the person was

simply asked to tie his shoe. After a significant delay, presumably for processing, the individual sat down in a chair, slowly brought his left leg to his right knee, and tied the shoe. Observation allowed for comment about probable range of motion impairments, at least, for the observed joints in movement, dexterity, trunk flexibility, strength of the left hip and knee flexors, fine and gross motor coordination, visual–motor integration, proprioception, and antigravity muscle groups during standing. There were no obvious impairments of gait other than speed. Flexibility of the trunk was demonstrated by reaching to tie the shoe during sitting. Obvious impairments of dexterity, possibly related to medication, were observed as well. It was also obvious that the individual was able to respond to a verbal command, was able to follow through, did not demonstrate evidence of apraxia, and was cooperative within his capabilities. When the ability to respond becomes more appropriate, more conventional testing can be performed and documented.[15–18]

The neurological rehabilitation field is currently responding to an increasing demand for assessment tools to provide better documentation of functional skills and outcomes.[16,19,20] Assessments such as the Barthel Index,[21] the Disability Rating Scale,[22] the Tuft's Assessment of Motor Performance (TAMP),[23] the Tinetti Performance-Oriented Assessment of Mobility,[24] and the Functional Independence Measurement (FIM)[25] have been utilized. Functional status measurements have been developed to measure performance during daily activity, which includes cognitive, social, and psychological functioning.[14] Therapists should be acquainted with a variety of measurement tools and should choose the most appropriate tool for the level of patient and the information desired. Rating systems provide ongoing comparative data to review the flow of progress. Computerized programs are available to not only document, but also graph an ongoing view of the course of treatment. By interval reviews of graphs or other visual aids, such as videotaping, the therapist provides a concrete tool for the patient to see if progress is being made or not. The therapist can take that opportunity to either encourage the patient to continue good effort or explore an alternative approach toward the desired goal.

Additional information can be obtained from pertinent family members.[26,27] Their insights about the individual's previous lifestyle and their perception of changes since the injury can reveal information that may help the therapist to understand and, perhaps, enhance motivation. Also, in appropriate situations, the family can be included in treatment sessions so as to educate and prepare them as potential participants in the person's future discharge environment.

During the initial interview, the therapist may wish to expand upon preadmission information by exploring the person's perception of the accident. Indications of retrograde or anterograde amnesia may be detected. If available, family members may provide their perceptions or additional insights for a confused or otherwise noncommunicative person. Documentation should include review of preinjury and postinjury history of fractures, surgeries, medications, and visual and/or auditory dysfunctions.

The subjective review should also include the individual's perception of current symptoms and any changes in activity levels that may be related to endurance, musculoskeletal complaints, sensorimotor deficits, pain, or vestibular dysfunction as they impact the person's quality of life. The person should also be asked to provide the therapist with an understanding of both short- and long-term goals for treatment. The Canadian Occupational Performance Measure© (COPM)[28] was developed by a group of OTs in 1991. It is a comprehensive, patient-centered method to document how the patient perceives him- or herself in the performance of multiple areas of life, including self-care, productivity, and leisure. This evidence-based outcome measure is designed to be administered during initial treatment sessions and repeated at intervals during the treatment program. The COPM© is found at http://www.thecopm.ca.

Range of motion, flexibility, and dexterity

A thorough evaluation and documentation of active and passive hip, knee, ankle, and cervical/lumbar spine ranges of motion must be conducted. Evaluation should also review upper extremity ranges of motion, including the shoulders, elbows, wrists, and fingers. If the initial screening finds near-normal active range values, assessment of passive range values will not be necessary. However, assessment of passive range values should be conducted on hemiparetic limbs. Documentation of flexibility (Figure 29.1) should include an assessment of the hamstrings, the gastrocnemius (with the knee extended), Thomas test, long sitting, trunk extension in the prone position, and trunk flexion from a seated position. Assessment of iliotibial band (ITB) flexibility should be included.

When evaluating upper extremity and hand function, hand dominance should be documented. Observe the person's ability to control gross grasp and release and perform lateral pinch, tripod pinch, and palmar prehension. Upper extremity and hand function are further observed for the ability to hold, stabilize, and carry a variety of both light and heavy objects. Gross motor coordination of the upper extremity can be documented during timed performance testing via the Box and Blocks Test of Manual Dexterity.[29]

Fine motor coordination and selective movements are assessed during timed performance tests (e.g., the Nine Hole Peg Test[30]) and through functional task observation. Such tests as the Purdue Pegboard[31] and the Minnesota Rate of Manipulation[32] can be used for advanced patient testing. If desired, additional prevocational assessments of dexterity, cognitive, and perceptual functions can be attained with such tests as the Crawford Small Parts Dexterity Test[33] and the Bennett Hand Tool Dexterity Test.[34] Objects that are pertinent to the patient's lifestyle should be used in the functional task evaluation (e.g., razors, toothbrushes, combs, buttons, zippers, eating utensils, pencils or pens, kitchen tools, cards, and work tools). Any complaints of

Flexibility evaluation		
	Left	Right
A. Hamstring	_____	_____
B. Thomas test	_____	_____
C. Gastrocnemius (knee extended)	_____	_____
D. Long sit test	_____	
E. Prone trunk extension	_____	
F. Seated flexion	_____	
G. Iliotibial band (ITB)	_____	_____

Figure 29.1 Flexibility evaluation form: Used to document information about the lower extremities and trunk.

pain or observations of edema, tremors, or changes in muscle tone should be documented.

Neurological examination

Although the comprehensive neurological examination takes place in the initial field evaluation and, subsequently, by other treatment professionals, this does not relieve the need for further assessment by the OT and the PT. A focused neurological examination is necessary to look at those components that will eventually be addressed by the OT and the PT.

SENSATION AND PROPRIOCEPTION

Although the structure of documentation varies in each clinical setting, a complete sensory evaluation should be performed (Figure 29.2). Tactile sensation is tested for light/firm and sharp/dull discrimination and hot/cold temperature discrimination. Responses should be recorded as intact or hyper-/hyposensitive. Proprioception testing includes the ability to name movements, mirror movements, and detect vibration. Graphesthesia (the ability to identify numbers written on the skin by the examiner's finger) and stereognosis (the ability to identify objects by touch) should be tested and documented. Record responses to proprioceptive testing as intact or impaired.

DEEP TENDON REFLEXES AND PATHOLOGICAL REFLEXES

These reflexes influence responses to movement. Record responses to the patellar, Achilles, biceps, brachioradialis, and triceps reflex tests as hyper (3+), normal (2+), hypo (1+), and absent (0) (Figure 29.3). The Babinski reflex should also be tested and recorded as present or absent.

CEREBELLAR TESTS

Cerebellar reflexes have significant influence on the performance of smooth movements. Tests should include performances of 1) finger-to-finger, 2) finger-to-nose, and 3) heel-to-shin. Record findings as normal, hypermetric, ataxic, or with intention tremor (Figure 29.4). Diadochokinesis is tested symmetrically and asymmetrically and is recorded as normal, ataxic, or unable.

Melnick[35] reported that the "little brain," located under the occipital lobe, has "more neurons than the rest of the brain put together" (p. 834). When the cerebellum and its connections are disrupted by traumatic or nontraumatic events, multiple deficits may be manifested. The most significant deficits are loss of motor learning and disabling ataxia. There is disorganization in rapid alternating movements and decreases in balance and central postural control. Intention tremor greatly impacts the ability to conduct daily activities. Other functions negatively impacted by cerebellar damage include speech and control of eye movement and gaze.

Urbscheit[36] discussed the frustration encountered by many therapists in the evaluation and treatment of cerebellar deficits. Many therapists are unable to adequately diagnose and treat cerebellar dysfunction. Swaine and Sullivan[37] reviewed inter-rater reliability for measurement of clinical features of finger-to-nose testing and reported fairly poor inter-rater reliability for determination of the presence of dysmetria. The therapist working with this population must become proficient in cerebellar evaluation and treatment. A recommended resource for therapists who will encounter such patients in the evaluation and treatment arenas is detailed in the chapter, "Movement Dysfunction Associated with Cerebellar Damage" by Morton and Bastian in Umphred's *Neurological Rehabilitation*, sixth edition.[10]

The individual must be observed for hypotonicity, dysmetria, difficulty with rapid alternating movements, and movement decomposition. These deficits may be observed in gait, pace of gait, and activities of daily living (ADL, e.g., brushing teeth, stirring food, eating, or trying to walk at a fast pace). Complaints of difficulties with vision while the

Neurological evaluation

I. Sensation

	Upper extremity		Lower extremity	
	Left	Right	Left	Right
A. Light/firm	Intact Hyper Impaired	Intact Hyper Impaired	Intact Hyper Impaired	Intact Hyper Impaired
B. Sharp/dull	Intact Hyper Impaired	Intact Hyper Impaired	Intact Hyper Impaired	Intact Hyper Impaired
C. Hot/cold	Intact Hyper Impaired	Intact Hyper Impaired	Intact Hyper Impaired	Intact Hyper Impaired

II. Proprioception

	Upper extremity		Lower extremity	
	Left	Right	Left	Right
A. Naming movements	Intact Impaired	Intact Impaired	Intact Impaired	Intact Impaired
B. Mirroring movements	Intact Impaired	Intact Impaired	Intact Impaired	Intact Impaired
C. Vibration	Intact Impaired	Intact Impaired	Intact Impaired	Intact Impaired
D. Graphesthesia	Intact Impaired	Intact Impaired	Intact Impaired	Intact Impaired
E. Stereognosis	Intact Impaired	Intact Impaired	Intact Impaired	Intact Impaired

Figure 29.2 Neurological evaluation form: Used to document sensory and proprioceptive functions.

Reflex testing

I. Deep tendon reflexes

A. Patellar				
Left	Hyper (3+)	Normal (2+)	Hypo (1+)	Absent (0)
Right	Hyper (3+)	Normal (2+)	Hypo (1+)	Absent (0)
B. Achilles				
Left	Hyper (3+)	Normal (2+)	Hypo (1+)	Absent (0)
Right	Hyper (3+)	Normal (2+)	Hypo (1+)	Absent (0)

II. Pathological reflexes

A. Babinski reflex		
Left	Absent	Present
Right	Absent	Present

Figure 29.3 Reflex testing form: Used to document reflex testing information.

Cerebellar tests				
A. Finger-finger				
Left	Normal	Hypermetric	Ataxic	Int. tremor
Right	Normal	Hypermetric	Ataxic	Int. tremor
B. Finger-nose				
Left	Normal	Hypermetric	Ataxic	Int. tremor
Right	Normal	Hypermetric	Ataxic	Int. tremor
C. Heel-shin				
Left	Normal	Hypermetric	Ataxic	Int. tremor
Right	Normal	Hypermetric	Ataxic	Int. tremor
D. Diadochokinesis				
Symmetrical	Normal	Ataxic	Unable	
Asymmetrical	Normal	Ataxic	Unable	

Figure 29.4 Cerebellar tests form: Used to document cerebellar functions.

individual is in motion may be related to cerebellar dysfunction as well as vestibular dysfunction.

Rapid, alternating movement evaluation

While seated, alternate floor touching with the heel and toe and seated side steps are observed for the number of repetitions performed in 10 seconds. The number of repeated standing side steps are also recorded for a 10-second period. Note quality of performance (Figure 29.5). These simple tasks can be good indicators of asymmetries or the ability to mimic a motor pattern as well as coordination of the lower limb.

Manual muscle test

The technique for manual muscle testing is well known by all qualified OTs and PTs. This assessment is performed not only to evaluate a muscle group's ability to produce force against gravity, but also the person's ability to isolate a muscle's movement and force. Manual muscle tests document strengths in musculature of the neck, shoulders, arms, hands, hips, knees, ankles, abdominals, and trunk extensors. In some situations, the manual muscle test may not be appropriate. For example, in the presence of spasticity, a forcefully opposing muscle group will increase muscle tone, and assessment of the ability to perform an isolated muscle contraction will not be valid.

Muscle tone

Most neurorehabilitation clinicians point to abnormal muscle tone as one of the major physiological barriers to full achievement of rehabilitation goals. Normal muscle tone allows the extremities and trunk to move through available ranges of motion from joint to joint. Abnormal muscle tone may be hypertonic or hypotonic. *Hypotonia* may result from a lower motor neuron or peripheral nerve injury. However, the more common cause of hypotonia seen in the neurorehabilitation clinic is a residual of traumatic brain injury (TBI) or stroke involving the cerebellum. Hypotonic muscles are less firm to the touch and demonstrate a lower resistance to passive stretch than normal. There is a limpness in the limb during passive ranging. Flaccidity is differentiated

Rapid alternating movement evaluation (number repetitions in 10 seconds)		
	Left	Right
I. Heel-toe:	_____	_____
II. Seated side steps:	_____	_____
III. Standing side steps:	_____	_____

Figure 29.5 Rapid, alternating movements form: A simple format for documenting rapid alternating movements.

from hypotonicity by the absence of voluntary, postural, and reflex movements with a loss of resistance to passive stretch.

Assessment of hypotonia starts with palpation of muscles and testing deep tendon reflexes. As mentioned, the hypotonic muscle lacks firmness. A pendular movement is seen when testing the deep tendon reflexes. Sitting posture at rest appears asymmetrical or limp. An object held in the hand may be dropped when the person is distracted. All fingers on the hand will flex when the individual attempts to flex only one at a time. A wet footprint is wider on the involved side.

Hypertonia, a term used interchangeably with spasticity, is one component of an upper motor neuron injury and may be a residual deficit from TBI. Spasticity, as defined by J. W. Lance,[38] is an increase in muscle tone due to hyperexcitability of the stretch reflex. Consideration must be given to the differentiation between spasticity and rigidity in an effort to determine the best treatment approach. Although spasticity is characterized by a velocity-dependent increase in tonic stretch reflexes, the increased tonic stretch reflexes in rigidity are not velocity-dependent. Spasticity typically involves a muscle on one side of a joint, but rigidity affects the muscles on both sides of a joint. Both hypertonia and hypotonia become problematic when the patient is unable to regulate the amount of muscle tone needed when activating various muscle groups. The residual problem is often very one-sided, either hyper-reflexive or hyporeflexive, resulting in mobility deficits at specific joints that interfere with functional activities.

The Modified Ashworth Scale (MAS)[39] and the Modified Tardieu Scale (MTS)[40] have been the most prominently used scales in the past. In the previous edition of this text, we reported that there was controversy regarding the "determination of the most reliable assessment format." At that time, studies to determine the most reliable scale provided no clear accord. The MAS and the MTS continue to be used, and more recent research has given them passing grades. Patrick and Ada[40] noted that the MTS "differentiates spasticity from contractures whereas the MAS is confounded by it" (p. 173).[41] A new scale, the Triple Spasticity Scale (TSS), has been researched by Li, Wu, and Xiong[42] and found to have good test–retest reliability and inter-rater reliability in the measurement of muscle tone. The TSS is reported to avoid some of the shortcomings of the previous scales. The one caveat to keep in mind is the one regarding the MAS issue with contractures. In the future, it is possible that the existing scales will be adjusted further or an entirely new scale could emerge.

During initial observations, many people may seem to have minimal to nil abnormal tone. However, the individual should be closely observed during active functional movements. This is another reason for evaluating the individual while he or she is performing functions in various environments. The evaluation should begin with an analysis of the motor control present in each extremity. Observations pertaining to lack of movement or minimal movement, in particular, in cases in which the dopaminergic system may have been impacted by the injury, may suggest the application of dopaminergic medication to enhance motor function. Conversely, persons who present with significant spasticity will generally not benefit from such an approach. The response of spasticity to stretching, relaxation, positioning, and medication requires exploration, together with an appraisal of the likelihood of response to chemical neurolysis and casting. Spasticity should be differentiated from rigidity in the hypertonic patient. Rigidity may respond to dopaminergic drugs whereas spasticity may be worsened. The PT and OT can provide quite valuable information to the physician in these arenas. The influence of emotion, pain, fatigue, and varying demands of motion and posture should be considered in evaluation of movement.

Muscle and cardiovascular endurance

Muscle endurance of the trunk and lower extremities is assessed by the PT. Trunk endurance (Figure 29.6) testing

Muscle endurance		
1. Trunk endurance		
Sit-ups	_____ repetitions	(1 minute)
Push-ups	_____ repetitions	(maximum)
Bridging	_____ seconds	(norm: 1 minute)
Hyperextension	_____ seconds	(norm: 30 seconds)
2. Lower extremity endurance		
Wall slide (90°/90°)	_____ seconds	(norm: 1 minute)

Figure 29.6 Muscle endurance form: Used to document trunk, lower extremity, and cardiovascular endurance.

documents the maximum number of sit-ups performed in 1 minute and the maximum number of push-ups the individual is able to produce. Bridging and hyperextension are each sustained as long as possible (Figure 29.6). Acceptable performance is considered to be 1 minute for bridging and 30 seconds for hyperextension. Cardiovascular endurance can be tested with a standard or modified Bruce™ test[43] (Figures 29.7 and 29.8) based on the individual's level of conditioning. It is very important to monitor heart rate and blood pressure during this exercise. Document the patient's current medications, which may affect vital signs at rest and during exercise. Advanced endurance testing, such as a physical capacity evaluation, may be performed to address back-to-work potential.

Differential diagnosis of cardiorespiratory endurance problems and vestibular dysfunction cannot be undertaken completely at this point in the evaluation; however, findings of nystagmus or other indicators during testing may point to vestibular dysfunction and should be noted for consideration during subsequent vestibular testing.

Mobility, posture, and gait evaluations

Although the majority of severely disabled TBI persons may have become quite mobile during the acute rehabilitation stay, there will be an occasional need for full evaluation of bed mobility, transfer, tub/shower, and wheelchair skills. In the residential setting, most people will be able to sleep in standard double size (or larger) beds. Bathrooms should be an appropriate size and equipped for wheelchair, walker, or cane mobility.

Cardiovascular endurance

Bruce's low level treadmill test
(modified Shefield-Bruce submaximal protocol™)

Stage	Time	Speed	Grade	METS	Date	Date	Date	Date	Date
Rest HR	xxxxx	xxxxx	xxxxx	xxxxx					
Rest BP	xxxxx	xxxxx	xxxxx	xxxxx					
Stage 1	Min 1 Min 2 Min 3	1.7 mph	0%	2.3					
Stage 2	Min 4 Min 5 Min 6	1.7 mph	5%	3.5					
RPE	xxxxx	xxxxx	xxxxx	xxxxx					
Stage 3	Min 7 Min 8 Min 9	1.7 mph	10%	4.6					
Stage 4	Min 10 Min 11 Min 12	2.5 mph	12%	6.8					
RPE	xxxxx	xxxxx	xxxxx	xxxxx					
Recovery _____ min	xxxxx	xxxxx	xxxxx	xxxxx					
Recovery _____ min	xxxxx	xxxxx	xxxxx	xxxxx					
Recovery _____ min	xxxxx	xxxxx	xxxxx	xxxxx					

Figure 29.7 Cardiovascular endurance form: Bruce's low level treadmill test.

Cardiovascular endurance									
Bruce's standard treadmill protocol									
Stage	Time	Speed	Grade	METS	Date	Date	Date	Date	Date
Rest HR	xxxxx	xxxxx	xxxxx	xxxxx					
Rest BP	xxxxx	xxxxx	xxxxx	xxxxx					
Stage 1	Min 1 Min 2 Min 3	1.7 mph	10%	4–5	hr				
Stage 2	Min 4 Min 5 Min 6	2.5 mph	12%	6–7	hr				
RPE	xxxxx	xxxxx	xxxxx	xxxxx					
Stage 3	Min 7 Min 8 Min 9	3.4 mph	14%	8–10	hr				
Stage 4	Min 10 Min 11 Min 12	4.2 mph	16%	11–13	hr				
Stage 5	Min 13 Min 14 Min 15	5.0 mph	18%	14–16	hr				
Stage 6	Min 16 Min 17 Min 18	6.0 mph	20%	17–19	hr				
RPE	xxxxx	xxxxx	xxxxx	xxxxx					
Recovery _____ min HR BP	xxxxx	xxxxx	xxxxx	xxxxx					
Recovery _____ min HR BP	xxxxx	xxxxx	xxxxx	xxxxx					
Recovery _____ min HR BP	xxxxx	xxxxx	xxxxx	xxxxx					

Figure 29.8 Cardiovascular endurance form: Bruce's standard treadmill protocol.

Beyond the expected physical components for bed mobilization and bed/tub/toilet transfers, other areas that impact mobility, such as cognitive abilities, safety judgment, impulsivity, visual deficits, and systems impacting postural control, should be observed and documented. The evaluation should document the person's ability to perform the tasks independently or with assistance and include notation of the quality of performance.

Bed mobility (Figure 29.9) explores scooting up and down as well as to the right or left sides. Is the person able to turn to either side and attain sitting and supine positions? A useful method to provide objective measurement of bed mobility is to time the task and document any observation of asymmetries between right and left sides. Note if the individual includes the hemiparetic side or is using compensatory strategies during movements. Is the person using some

Mobility evaluation

I. Bed mobility		Assist	Quality
A. Scooting			
1. Up			
2. Down			
3. Left			
4. Right			
B. 1/2 rolls			
1. Left			
2. Right			
C. Attain sitting			
D. Attain supine			

II. Wheelchair mobility		Assist	Quality
A. Even surfaces			
B. Uneven surfaces			
C. Inclines			
D. Declines			
E. Doorways			
F. Curbs	_____ inches		

III. Transfers	Assist	Quality
A. Preparation		
B. Wheelchair to level surface		
C. Wheelchair to elevated surface		
D. Wheelchair to floor		
E. Floor to wheelchair		

IV. Ambulation	Assist	Quality
A. Sit to stand		
B. Assistive device		
C. Indoors		
D. Outdoors		
E. Uneven terrain		
F. Inclines/declines		
G. Curbs		
H. Stairs		

Figure 29.9 Mobility evaluation form: Used to collect information on bed, wheelchair, transfer, and ambulation activities.

aspect of abnormal tone to achieve movement? For example, extensor thrust may be used to complete rolling. Note differences in bed mobilization abilities on a gym mat versus a soft bed in the residential setting. Quality of movement should be emphasized. Wheelchair mobility (Figure 29.9) assessments include the patient's ability to mobilize on even and uneven surfaces, inclines and declines, through doorways, and over curbs. Note the approximate height of the curb and time to cover specific distances.

Document the person's preparation for transfer (Figure 29.9). Record any need for verbal and/or physical cues as well as the need for physical assistance. Note performance in transferring from the wheelchair to a level surface, an elevated surface, the floor, and floor to wheelchair.

Observations of the general ability to ambulate should be documented (Figure 29.9) whether the individual has detectable mobility problems or appears quite normal. The evaluation should include observations from clinical, residential, and community settings. Observe and document ambulation indoors, outdoors, on uneven terrain, on inclines and declines, and negotiating curbs and stairs. Document the ability to rise from sitting to standing. Note the need for assistance and the use of any supportive devices. The patient may move about a well-lit, even-surfaced, clinical setting without apparent difficulty. Observe the patient moving in areas with low-light and uneven terrain (e.g., darkened room with plush carpeting or evening time on grass/rocky terrain). Less obvious impairments in sensorimotor and/or vestibular system–related performance may be revealed under more realistic and demanding circumstances. The evaluation may even be extended to include movement onto or off of escalators

and into or out of elevators. Watch for a tendency to avoid or complain about tasks in noisy or busy environments. Subtle changes in fluidity of body movement during ambulation can point to potential vestibular, cerebellar, or oculomotor problems.

During ambulation evaluations, document reduced or absent reciprocal arm swing, slowed pace of walking, reduced head turning or visual scanning, drifting or "wall-walking," and slight or obvious hesitancy when changing directions. It is also important to note subjective complaints of dizziness, nausea, or feelings of drunkenness or lightheadedness when walking. These may be additional indicators of visual and/or vestibular disturbances.

Notations should be made regarding the patient's posture during sitting and standing activities as well as any gait deviations.[44] Observations should also note apparent influences from muscle weakness; leg length discrepancies; pain; vestibular, cerebellar, or ocular dysfunctions; cognitive or perceptual deficits; poor endurance; loss of flexibility; and impairments in somatosensory functions.[36,45–48]

As emphasized in neurodevelopmental treatment (NDT),[1,49] observations of postures should include the position of the scapula, pelvis, rib cage, and spinal column. Position of the trunk may vary greatly, so also note the conditions under which observations are made. For example, is the individual sitting on a solid surface or on a bed or standing? Note if the person is able to recognize and maintain midline with head and trunk positions.

Vestibular evaluation

Three systems are required to maintain spatial orientation and balance while moving about the environment. These are the visual system, vestibular system, and the somatosensory system (proprioception). Information from each system is gathered and processed through neuronal pathways with information from the other two systems. This normally results in a coordinated effort to maintain uprightness or orientation in space during a variety of activities. Dysfunction in one or more of these systems can greatly handicap the patient. During the initial PT/OT evaluations, the patient may have complaints of dizziness and difficulty keeping balance when turning the head to one side or the other while walking. Looking up or down, rolling over in bed, or arising from the supine position may provoke symptoms.[50,51]

During the initial evaluation, the therapist may use a variety of checklists to pinpoint areas of difficulty. These include the Motion Sensitivity Quotient (MSQ),[52] the Dizziness Handicap Inventory,[53] the Functional Reach Test,[54] and the Fukuda Stepping Test (Unterberger's). Checklists can be found in the EDGE database: http://www.rehabmeasures.org under the link: Instruments.

More complex problems related to the vestibular system should be referred to a neuro-otologist for a formal evaluation. Identifying the specific cause will be important in identifying the specific treatment required to resolve the problem. Therapists with vestibular rehabilitation training are best qualified for the task.

Sensorimotor integration and dynamic balance evaluation

In a normal central nervous system, purposeful activity of the extremities depends upon the stabilization of the trunk. When postural control is maintained, significant influence is exerted on limb tone, range of motion, and control.[44] However, the individual with moderate-to-severe sensorimotor impairment may find that extremity movement is less than functional when selective movement is reduced to gross movement patterns influenced by primitive reflexes.

As previously mentioned, the ability to maintain standing balance in static or dynamic conditions requires the complex interaction of vision, vestibular, and somatosensory systems. However, these systems must be coupled with appropriate motor programs, muscle contractions, body alignment, and ranges of motion to allow for smooth and well-coordinated, purposeful movements.

Observe body alignment in the sitting position. Note responses to weight shifting in lateral and anterior/posterior directions while sitting. Note the direction of shift while the individual orients the head, rights the trunk, or resumes the vertical position. Notice responses of dizziness, disequilibrium, and protective responses.

The Tinetti Performance-Oriented Assessment of Mobility[24] allows assessment of balance deficits in more impaired patients during movement in functional tasks. The assessment calls for observation of the patient during sitting, arising, standing, and walking. Balance reactions are also observed while the individual turns around (360°), sits down, and attempts single-foot support. The test provides a scoring system for comparative data. As the patient reaches scoring criteria, he or she can be advanced to more challenging balance exercises if desired.

A more recent assessment to identify subtle deficits in balance while the patient is engaged in mobility activities is the BESTest[9] (Balance Evaluation Systems Test). This very comprehensive tool was developed by Faye Horak, PhD, PT, director of the respected Balance Disorder's Laboratory at Oregon Health and Science University (OHSU). The BESTest is considered to be sensitive and quantitative and more likely to result in third-party reimbursement. A slightly abbreviated form, the Mini-BESTest,[55] is also available. The test is appropriate for patients at any age with significant ambulatory deficits related to TBI, cerebellar ataxia, vestibular disorders, MS, stroke, CP, or other balance disorders. Many aspects of other balance tests, such as the Timed Up and Go (TUG), are incorporated in this one assessment system.

The BESTest© and Mini-BESTest© can be found with detailed instructions for each section including scoring instructions at http://www.bestest.us.

An example of the contents of the BESTest© with its four major categories, each with three levels of grading, and the TUG test is as follows:

a. The Anticipatory Section involves 1) sit to stand with arms crossed over the chest, 2) rising on toes, 3) standing on one leg.
b. The Reactive Postural Control Section involves 1) compensatory stepping correction: forward, backward, and lateral.
c. The Sensory Orientation Section involves 1) stance with eyes open, on a firm surface; 2) stance with feet together, eyes closed, standing on foam surface; 3) standing on an incline with eyes closed.
d. The Dynamic Gait Section involves 1) walking gait speed, 2) walking with head turning horizontally, 3) walking with pivot turns, 4) stepping over obstacles.
e. Timed Up and Go (TUG) with dual tasks.

The Hendrich II Fall Risk[56] assessment can be helpful in identifying patients who may be at risk for falls. This assessment considers the patient's level of cognition, influences of medications, behavior, gender, and emotional state. Although it is yet another tool that was designed for the older population, it also applies to many patients in the brain-injured population.

Hendrich II Fall Risk model–modified

Characterize the individual's condition according to the listed condition and put the corresponding number of points in the last column. If the total number of points is > 5, the patient is a high risk for falls. Circle yes/no for each additional factor.		
Confusion	Charted as "confused or disoriented"	4
Disorientation	or score of < 17 on Mini-Mental Exam	
Symptomatic depression	Charted as "depressed" or score of < 8 on Koenig II Depression Rating Scale	2
Altered elimination	Charted with altered elimination needs of a "yes" response to Bender Elimination Test	
Dizziness/vertigo	Charted with dizziness or vertigo	1
Male gender		1
Antiepileptics	Tegretol, Depakote, Neurontin, Dilantin, Depakene, Depakote	1
Benzodiazepines	Xanax, Klonopin, Valium, Ativan, Dalmane, Versed, Restoril	1

Get up and go test

Able to rise in a single movement, no loss of balance with steps	0
Pushes up, successful in one attempt	1
Multiple attempts but successful	3
Unable to rise without assistance during test	4
Total Score	–
A score of 5 or greater = high risk	

Assessment of smell and taste

It is imperative that assessments of olfactory (smell) and gustatory (taste) senses are included in the overall evaluations by the OT or PT. Impairment or absence of smell can occur in mild-to-severe TBI depending upon the focus of injury. In terms of rehabilitation interest, the focus of attention is typically given to the sense of smell. Olfactory dysfunction may have gone undetected until the individual reaches the postacute phase of treatment. Anosmia is thought to occur in approximately 5.5% of the TBI population, and over a third of TBI patients have dysosmia.[57,58] As many as a third of people with TBI may have difficulty with olfactory naming and recognition. Questions should be raised by complaints of smelling foul odors, poor appetite, or unawareness of body odor or various household smells, including burning or spoiled foods.

It is estimated that disturbances in olfaction occur in approximately 20% of head traumas with damage to cranial nerve I (olfactory nerve) or in the orbitofrontal area of the frontal lobe.[59] The University of Connecticut Health Center's Taste and Smell Clinic (www.uchc.edu) estimated that approximately 0.5% of the TBI population suffered loss of taste. Some patients may not be aware of change in these senses. However, the individual who is aware may have no understanding of the implications of such an impairment on daily life. For this reason, the patient and family must be educated about hazards related to impaired function in taste and smell.

Changes in the ability to detect smells may occur with or without fracture injuries to the bony structure of the face. Fracture injuries may result in shearing of some or all of the olfactory axons that protrude through the cribriform plate of the ethnoid bone above the nasal cavity posterior to the bridge of the nose. As the odor is taken up the nose, the olfactory axons capture and transmit the odor signal above the cribriform plate and into olfactory bulbs of the olfactory nerve. The odor signal may be transmitted along the olfactory nerve through branches into the thalamus or other areas of the internal capsule before being relayed into the olfactory cortex (orbitofrontal cortex). Factors involved in emotion and motivation may be impacted when olfactory signals mediated through the amygdala and hypothalamus are impaired. An inability to discriminate odors occurs when lesions are found in the orbitofrontal cortex.[60]

The complete loss of smell (anosmia) occurs when bulb shearing has occurred. An altered or distorted perception of odors (dysosmia) may occur when damage is in the orbitofrontal cortex. A favorite food may be perceived as smelling foul (parosmia).

Taste is detected by taste cells in the mouth involving the tongue, palate, pharynx, epiglottis, and upper third of the esophagus. Taste buds on the tongue detect molecules on the anterior two thirds of the tongue through the taste fibers of cranial nerve VII (facial nerve). The afferent portion of cranial nerve IX (glossopharyngeal nerve) controls the sense of taste for the posterior one third of the tongue. The palate taste buds are innervated by a branch of cranial nerve VII and the epiglottis and esophagus by branches of cranial nerve X (vagus nerve). Taste sensory fibers enter the medulla of the brain stem and transmit into the thalamus. Gustatory functions detect four basic stimuli: bitter, salty, sour, and sweet. Taste buds responding to each of the four basic stimuli are found in all regions of the tongue. Most food flavors are derived from information coming through the olfactory system. Molecules are sent into the back of the nasal cavity by cheeks, tongue, and throat movements.

Following a chemosensory screening by OT or PT, alterations in function should be examined in light of the original injury. The patient's medical history should be explored to consider any type of respiratory problem or allergies. In some cases, a loss or partial loss of smell may be transitory in nature. An easy manner to assess smell function can be obtained by presenting some familiar odors to the patient. Unlabeled items, such as vanilla, coffee, chocolate, and lemon, are often used for this rough assessment. A very quick estimate of sense of smell can be obtained by placing an alcohol pad under the patient's nose.

A more extensive and quantitative assessment of smell function can be obtained with the Smell Identification Test, developed by the University of Pennsylvania (UPSIT).[61] The test consists of four packets, each containing 10 "scratch-and-sniff" odorant strips. Above each strip is a multiple choice of four possible responses. A test booklet lists the correct answers and provides a table to determine the degree of olfactory loss as based on the age and sex of the patient in addition to the number of correct responses.

The individual will require awareness and education in ways to detect smoke, gas, other toxic fumes, and spoiled foods.[62,63] A chemosensory screening may also indicate the necessity to refer for additional clinical examinations by an otorhinolaryngologist or neurosurgeon.

Evaluation of vision

The incidence of visual dysfunction following TBI is fairly high. Schlageter et al.[64] reviewed 51 patients within days of admission. They found that 30 (59%) were impaired in one or more of the following: pursuits, saccades, ocular posturing, stereopsis, extraocular movements, and near/far eso–exotropia. Because the acute rehabilitation experience has become increasingly shorter in duration for this population, relatively little attention is paid to visual–motor and visual–perceptual remediative efforts. As a consequence, these deficits are frequently evidenced in rehabilitation settings.

A thorough OT evaluation should include a complete vision screening test.[65] Prior to the vision screening, preliminary information is collected via the Visual Symptoms Checklist (Figure 29.10). This questionnaire not only collects subjective responses, but it provides an opportunity for objective documentation. For example, the individual may be aware of symptoms. However, the therapist may observe head tilting, squinting, or closing an eye, difficulty reading, or bumping into walls or furniture on one side.

The screening should include visual attentiveness, near and distance acuities, ocular pursuits, saccades, near point convergence, eye alignment, stereopsis, color identification, and peripheral fields. Changes in acuities may be reflected in difficulty performing tasks requiring near vision (e.g., shaving or putting on makeup) or difficulty recognizing environmental cues (e.g., facial expressions).

Smooth ocular pursuits are required for such tasks as reading a line of print or a column of words or numbers. Saccades provide a rapid but accurate shift of the eye in such visual tasks as reading to the end of a line of print and rapidly shifting leftward to the beginning of the next line. The King-Devick Test[66] measures scanning and saccadic function required to read detailed and structured formats (e.g., reading a bus or train schedule). Evaluation of visual system integrity may raise suspicion of vestibular or cerebellar dysfunction. Impairment in near point convergence is another tracking deficit that may be manifested in double or blurred vision and decreased depth perception.

Strabismus may result in double or blurred vision as the eyes move through the visual sphere. The ability to visually scan may be impaired in such tasks as reading, writing, grocery shopping, driving, or reviewing a map. Eye alignment measures horizontal and vertical alignments to detect possible deviations.

Deficits in stereopsis impact many functions requiring depth perception. The ability to judge spatial relationships in such eye–hand tasks as threading a needle, targeting food on a plate, or negotiating stairs is affected by this deficit.

Peripheral and central vision are required for a full field of vision. A loss of the peripheral field(s) will impact safety for ambulation, awareness of environment, and safe driving and will require the patient's awareness and ability to compensate with appropriate head turning.

Following the vision screening, appropriate referrals to the neuro-ophthalmologist or neuro-optometrist may be required for further in-depth assessments. (Refer to chapters in this text by Suter for in-depth discussion of evaluative and treatment options.)

People with TBI may or may not complain of visual disturbances. However, behavioral evidence of oculomotor deficits may be seen in problems with reading, writing, driving, playing video games, or watching television. As the therapist asks more specific questions, patients may report that words "jump" around on the page or that they

Visual symtoms checklist

Prescription glasses: Yes_____ No_____

If yes: Were glasses worn prior to injury?_____
Since the injury only?_____
Last vision examination?_____
New prescription?_____Date:_____

Answer **yes** or **no** to the following questions:	Yes	No
1. Do you have blurred or double vision?	_____	_____
2. Do you tilt your head to see more clearly?	_____	_____
3. Do you squint or close an eye to see?	_____	_____
4. Do you get a headache while reading, watching television, riding in or driving a car? Other?_____	_____	_____
5. Do your eyes feel "tired"?	_____	_____
6. Do you lose your place while reading?	_____	_____
7. Do you hold objects or reading material close to see?	_____	_____
8. Do you avoid reading or not read as often as you did before the injury?	_____	_____
9. Do you miss words, letters, or numbers while reading?	_____	_____
10. Do you have difficulty distinguishing colors?	_____	_____
11. Do you avoid dark areas or avoid driving after dark?	_____	_____
12. Do you sometimes confuse which direction is right or left?	_____	_____
13. Do you reverse letters, numbers, or words?	_____	_____
14. Do you have difficulty recognizing road or street signs before it is too late to turn?	_____	_____
15. While you are standing still, do objects seem to jump or move?	_____	_____
16. While you are walking, do objects seem to jump around?	_____	_____
17. Do you bump into objects on one side or the other?	_____	_____

Figure 29.10 Visual symptoms checklist: Used to collect information on vision from the patient.

frequently lose their place while reading. They may complain that they can read for only short periods of time. They may relate that images move in strange ways while watching television or while driving. They may experience dizziness, headaches, or nausea during these activities. Head position adjustments can foretell oculomotor problems as can observation of dysfluencies of gait, especially in uneven terrain, such as curbs, uneven sidewalks, stairs, or multilevel surfaces. Often, a person will complain of neck and shoulder problems that might actually be vision driven versus purely orthopedic difficulty.

The field of vision therapy represents a valuable evaluation and treatment process that has been practiced by too few over the years. Although a few OTs working with patients in neurorehabilitation clinics have been trained in vision therapy, the majority of certified vision therapists are found in vision rehabilitation clinics under the management of neurologic optometrists (see chapter by Suter).[67,68]

Visual perception and perceptual motor evaluation

Vision areas frequently requiring intervention following brain injury include the optic systems (i.e., gross ocular skills, scanning, alignment, etc.), visual pathways (i.e., field cuts), visual perception, visual attention, and visual motor integration. The hierarchy of visual skills means that any component that is impaired, such as gross ocular skills, will most likely impact more complex skills, such as visual perception. A thorough evaluation will provide the opportunity to apply the appropriate modalities to remediate impairments related to vision and visual perception. Because the visual system is a "silent system," many visual deficits may not be observable. For this reason, it is necessary to have a skilled clinician evaluate the status of visual perception and perceptual motor in an effort to identify impaired components.[69–71]

Visual perception examines visual figure–ground, form constancy, spatial awareness or position in space, depth perception, visual memory, visual sequential memory, visual–motor integration, and spatial relationships. *Visual figure–ground* is the ability to distinguish foreground from background, and *form constancy* explores the ability to perceive subtle variations in form. *Position in space* is the ability to manage such spatial concepts as in/out, up/down, and front/behind. *Spatial relationships* examines the individual's ability to perceive positioning of two or more objects in relation to themselves or other objects. It is easy to understand how frequently the patient requires these functions in everyday living.

Clinical evaluations of visual perception should include such tests as the Motor-Free Visual Perception Test–Vertical Format (MVPT-V).[72] The MVPT measures the time it takes to process visual information and react to that information. In vertical, it helps to eliminate errors that may be caused by hemianopsia or visual neglect. This information applies to such tasks as reading comprehension, depth perception for ambulation, and driving. Standardized scores are compared among individuals without head injuries, individuals with head injuries but not a visual neglect, and those with a head injury and a neglect.

Advanced standardized perceptual tests, such as The Test of Visual–Perceptual Skills (nonmotor)–Revised (TVPS-R),[73] greatly enhance previously available detail and precision. The norms were based on developmental ages for perceptual skills.

The Hooper Visual Organization Test[74] examines the ability to organize visual stimuli by showing pieces of an object. These skills are needed to locate items in a grocery store, refrigerator, or in a cupboard for example. The Hooper Visual Organization Test is useful in detecting deficits in the right hemisphere and will determine actual perceptual deficits aside from performance.

An evaluation of the ability to perform purposeful movements on command or praxis is important for all people with TBI. Apraxia or dyspraxia may be obvious or subtle and may influence physical performances. Even in the person with mild TBI (MTBI), initiation and sequencing of functional motor acts need close observation for potential disorganization.[75] Skills required to produce a design in two and three dimensions (e.g., assemble various items from written or illustrated instructions) relate to constructional praxis and block design. Form perception is assessed via the form board and examines the ability to differentiate variations in form.

Difficulties in identifying body parts or in right/left discrimination impact perception of body self or scheme. The OT can assess these abilities with the Draw a Person, Body Part Identification, and Body Puzzle tests.[76]

Lezak[77] warned that observations must distinguish between perceptual failures, apraxias, spatial confusions, motivation, or attention problems. Therapists have, more recently, responded to this need for clearer definition of deficits and better direction for treatments. In this regard, Bowler[70] noted that two assessments are beginning to be utilized to define perceptual skills and other neurological skills that contribute to overall function. The Rivermead Perceptual Assessment Battery[78] assesses deficits in visual perception and was developed for adults with brain injury. The Lowenstein Occupational Therapy Cognitive Assessment[79] examines orientation, perception, visuomotor organization, and cognition and provides baseline information for treatment. Although some areas of assessment overlap, the combined tests view each function from a variety of perspectives to more distinctly define deficits.

Assessment of activities of daily living

The OT is able to gather meaningful information from observations during actual daily tasks in the residential treatment setting or the person's home. The structure of some programs allows a trained rehabilitation assistant to gather appropriately documented data of several specific tasks over several days during the initial assessment. This documentation continues throughout the program for the purpose of reassessment or as feedback data. For example, observations of the manner in which the individual organizes and sequences tasks and manages time can be documented while the person plans a meal, shops for items, and prepares a meal. This continually collected data directs the OT along a progression of therapeutic focus, clinically and residentially (Figure 29.11).

ADL assessment may also include an evaluation of the living environment in which the person resides. Home modifications, environmental controls, and adaptive equipment needs should be addressed to maximize independence and safety. Training and education may be provided concerning energy conservation techniques, transfers within the home, and emergency alert systems. An evaluation of the community is also helpful to identify resources for vocational or leisure exploration. Community transportation needs may also be addressed.

Take careful note of potential dependency behaviors. The family or others may fail to recognize that tasks are innocently assisted or completely performed by them for the injured person. If possible, assess ADL skills in a normal living environment, independent of family interaction. This approach should help to identify true problem areas and can be a good time to educate the individual and family about observed deficits and needed intervention for same.

Concomitant injuries

ORTHOPEDIC AND SPINAL CORD

Therapists will encounter people with TBI who have accompanying orthopedic and/or spinal cord injuries. Special orthopedic issues, such as heterotopic ossification, must be appropriately addressed.[80] Regardless of the possibility that surgical intervention may or may not be involved, the PT and the OT will play a vital role. In a postoperative

Activities of daily living checklist

Assistance levels

0 = no assistance required to initiate, continue, or complete task
1 = minimal verbal cues or gestural prompts
2 = intermittent verbal cues or gestural prompts
3 = minimal physical prompts
4 = intermittent physical prompts
5 = guided performance
6 = unable

Dressing Date:_____

	Level	Comments
1. Don shirt/blouse/dress		
2. Doff shirt/blouse/dress		
3. Don underwear		
4. Doff underwear		
5. Don pants		
6. Doff pants		
7. Buttoning (small, large)		
8. Zipping (tops, pants)		
9. Buckle/unbuckle belt		
10. Don/doff socks/hose		
11. Don/doff brace/splint		
12. Accessories on/off		
13. Shoe on/off		

Grooming/hygiene Date:_____

	Level	Comments
1. Use faucets		
2. Wash face/hands		
3. Use handkerchief/tissue		
4. Apply/remove glasses		
5. Brush teeth/clean dentures		
6. Brush/comb hair		
7. Shampoo hair		
8. Style hair		
9. Shave face/legs		
10. Apply deodorant		
11. Apply make-up		
12. Care for nails		
13. Manage clothes at toilet		
14. Cleans self at toilet		
15. Manages feminine hygiene		
16. Bathe/towel dry entire body		
17. Skin inspection		

Figure 29.11 ADL checklist: Used to document daily performance of ADLs. This information is used by staff to produce weekly and monthly reports of the patient's progress. (*Continued*)

situation, therapeutic follow-up will be necessary to prevent loss of flexibility and function. Botte and Moore[81] describe, in detail, the methods for acute orthopedic management of extremity injuries. They point out the importance of anticipation of uncontrolled limb movement, avoidance of joint immobilization, and avoidance of prolonged traction methods. In the majority of cases, the acute orthopedic issues will have received adequate attention from medical staff.

At the acute level, musculoskeletal injuries are missed diagnoses in approximately 10% of individuals arriving at head trauma units.[82] As people are moved at an increasing pace through the acute phases of treatment, therapists are faced with greater demands for orthopedic management. Monitoring of proper positioning, modalities, splinting/casting, sensation, mobility, and pain management is necessary. The therapists will need to educate the injured person, the family, and other therapeutic staff in the possible adjustments required to allow an optimum of function.

Review of frequency of musculoskeletal injury[81] shows that the shoulder girdle, radius, and ulna are among the most common upper extremity injuries. The elbow must be watched because of frequent spasticity around the joint, development of heterotopic ossification, and possible ulnar neuropathy. Fractures of the humerus are relatively rare.

Household cleaning Date:

	Level	Comments
1. Change sheets/make bed		
2. Pick up objects from floor		
3. Dust		
4. Sweep/mop/vacuum		
5. Transport pail of water		
6. Wring out mop		
7. Clean windows		
8. Clean refrigerator/stove		
9. Put out garbage		

Laundry Date:

	Level	Comments
1. Sort clothes		
2. Use washer/dryer		
3. Use detergent		
4. Hand launder		
5. Put clothes on hangers		
6. Fold clothes		
7. Put clothes away		
8. Iron clothes		

Meal planning Date:

	Level	Comments
1. Plan balanced meals		
2. Scan kitchen for necessary items		
3. Compile grocery list		
4. Estimate amount of money needed		
5. Get to/from store		
6. Locate items in store		
7. Retrieve items from shelves		

Meal preparation/cleanup Date:

	Level	Comments
1. Read recipe/directions		
2. Follow recipe/directions		
3. Remove food from refrigerator		
4. Remove items from cupboard		
5. Organize and transfer items to work area		
6. Open packages/cans/bottles		
7. Handle pots/pans/utensils		
8. Use faucets		
9. Pour liquids (hot/cold)		
10. Use microwave		
11. Use stove		
12. Use oven		
13. Peel/cut vegetables		
14. Break eggs		
15. Stir		
16. Measure		
17. Use timer/clock		
18. Set table/clear table		
19. Transfer food/liquids to table		
20. Wash/dry dishes		
21. Load/unload/use dishwasher		
22. Wipe stove/microwave/table		
23. Put dishes away		

Figure 29.11 (Continued) ADL checklist: Used to document daily performance of ADLs. This information is used by staff to produce weekly and monthly reports of the patient's progress.

Fracture of the femur is most common, followed by fracture of the tibia in the lower extremities. Pedestrian accidents often involve the pelvis. Injuries to the acetabulum and hip are comparatively rare.

There are occasions when a traumatic event involves both brain injury and spinal cord injury. The subject of spinal cord injury assessment and treatment is not discussed in this chapter; however, the point to be made involves the occasion of moderate-to-severe TBI and concomitant spinal cord injury. In the acute phase of care, the potential for significant complications is present. However, as neuromedical stability occurs, the patient will be a candidate for acute rehabilitation to address both spinal cord and brain injury residuals. The next expected phase will be a transition into a postacute neurorehabilitation program experienced in the postacute treatment needs of the patient with the dual diagnosis of spinal cord and brain injury. This assures that cognitive, behavioral, and psychological aspects will be addressed along with the physical aspects of living with paraplegia or quadriplegia. A normalized residential setting provides environmental validity while the patient adjusts and transitions toward a new lifestyle. From the beginning, every neurorehabilitation discipline must be involved as a united team with three goals: 1) a thorough assessment of all functions, 2) a well-managed treatment approach to advance the individual's ability to function at the highest possible level, and 3) preparation for a smooth transition into the discharge environment.

In some cases, the traumatic event results in spinal cord injury but without initial evidence of significant cerebral injury. However, as the individual becomes more active, evidence of MTBI may appear. Such problems as memory, concentration, vision, spatial orientation, behavioral changes, or others may be observed. In this regard, additional assessments may lead to a diagnosis of MTBI.

TMJ DYSFUNCTION

Another frequent concomitant injury is that of the temporomandibular joint (TMJ). TMJ dysfunction may arise from an associated facial injury or cervical myofascial injury.[83] Mechanisms of injury associated with MTBI can produce minor-to-severe TMJ dysfunction. TMJ problems may manifest by headaches (described as fan shaped in radiation in proximity to the joint); jaw, neck, or back pain; eating problems; or subtle postural disorders. As a matter of awareness and thoroughness in the evaluation process, the PT evaluation should include a TMJ screening assessment. If the neurological therapist is not trained in treatment of TMJ dysfunction, appropriate referrals can be made for in-depth examinations and potential treatment. Some PTs are trained and work with dentists in assessment and treatment of TMJ-related problems. Although pain behavior related to this dysfunction can represent a hindering factor to an efficiently addressed TBI rehabilitation program, TMJ dysfunction is often ignored. It is important to keep in mind that visual and vestibular deficits may be associated with TMJ pain; therefore, careful screening in all areas is needed to fully address these complaints.

PAIN

Pain behaviors, in general, can be frequently seen in individuals with MTBI than in more severely injured people. In fact, the existence of mild brain injury can actually be hidden by pain behaviors.[84] Headaches are a common focus of the MTBI patient.[85] Pain, whether real, exaggerated, or imagined, is pain and, along with companion emotional issues, can become a large obstacle to progress.

Perhaps the most frequent complaint of pain arises from headache.[86] Headache, however, can arise from a number of etiologies.[87] It is important to differentiate headaches arising from TMJ dysfunction from those arising from sinusitis. Injuries to the head often include injury to the sinuses. These headaches typically localize around the eyes and maxillary region in a mask-like distribution. Headaches that are occipitally and/or frontally located may represent tension headaches arising from muscular tension in the neck and shoulder musculature. The patient who complains of daily headache may benefit from review of medications or substances that are known to cause rebound headache.

Headaches that arise from muscular tension or TMJ dysfunction may be improved by physical therapy for those problems. The etiology for the muscular tension must be determined as to whether it arises from musculoligamentous strain, orthopedic injury, visual disturbances, or compensatory reaction to vestibular hypersensitivity.

In management of pain, utilize a system that allows for the patient to rate the pain experience throughout the day. Additionally, concomitant recording of the degree to which pain impacts the person's ability to function is useful. These reference points can be utilized by the treating physician and team to determine appropriate medication and therapeutic approaches. Therapeutic approaches available include thermal treatments, ultrasound, massage, flexibility exercises, strengthening exercises, and relaxation. In some cases, pain management may be enhanced by involvement of psychological services for the individual to explore relaxation or hypnosis as potential avenues of treatment. Fortunately, the vast majority of pain management programs for TBI respond well to conservative modalities of treatment, either in isolation or in combination.

It should be understood that the brain-injured person may tend to perseverate on a painful extremity, cast, etc. The therapist must be sympathetic and pursue appropriate investigations into potential causes and treatments; however, the therapist should also be aware that the problem may appear to be larger than it truly is. It is for this reason that behavioral observation of activity restriction caused by pain can be useful in addition to the person's report.

Driving

Driving is a very complex and dangerous ADL. It requires a person to process, plan, and respond while managing

the moving components of a car that is constantly moving through a dynamic environment of potential hazards. The ability to drive can be dramatically impacted by impairments in or damage to interconnections between the vestibular, ocular, physical, and psycho-emotional systems. The rate at which the car and the environment change will demand immediate and accurate visual, vestibular, cognitive, physical, and behavioral responses. Lack of adequate integration and responses from these systems can result in death or life-long disability.

Driving is a privilege in our society although it is often viewed as a right. It is symbolic of independence. It reduces the barriers to community integration, including meaningful activities outside of the home. Restrictions in driving have a profound social impact on a person. Without access to driving, a person may experience financial implications associated with joblessness, isolation, and diminished ability to assimilate into a community. Restricted drivers may rely on family or friends who are able to assist for the short-term but perhaps not for the long-term.

Many inaccurate perceptions about driving exist among individuals with brain injury and their families. They may believe that the mere physical possession of a license indicates that driving privileges have not been revoked or suspended after injury. Health professionals may fail to inform the Department of Motor Vehicles (DMV). Therefore, the injured person may have the perception that he or she is safe or cleared to drive and may lack the insight to restrict him- or herself. Family or friends may clearly see that driving will pose significant problems for the injured person and others. For this reason, interviews during rehabilitation assessments should not be limited to the injured person, but should include family members and/or friends.

Information regarding driving behavior may be revealing. For example, are there times of day or night or certain areas that the individual avoids driving? Does the person get lost more often than usual? Does the driving behavior show impulsiveness and poor safety awareness or judgment? Does dizziness occur? Is anxiety increased when driving? Confusing visual perceptions, movement imperceptions, and spatial disorientation can produce frightening and disabling effects.[65,87–89] An interview of the injured person may not be adequate when the traumatic injury has involved the frontal lobes. Poor insight or loss of insight is a frequent deficit exhibited after frontal lobe injury, and the person may fail to recognize the functional implications because they believe they have the necessary skills to drive. Studies have reported that 39%–46% of those who sustained a severe brain injury return to driving; however, only 24%–37% of those who returned to driving participated in a formal driving assessment.[90,91]

Return to driving after acquired or TBI mandates a comprehensive evaluation by multiple disciplines. Evaluative information is collected by an ancillary team involving the individual's family and friends, OT, occupational therapy assistant, speech/language pathologist, PT, neuropsychologist or psychologist, audiologist, therapeutic recreation specialist, social worker, nurses, physicians, orthotist, prosthotist, seating specialist, developmental optometrist, ophthalmologist, and the DMV at the state level.[92]

The actual driving component is then addressed by the primary team involving the injured individual and caregivers, an OT driving specialist, a vehicle modifier, physicians, and the case manager. A comprehensive driver screening must be completed prior to attempting a behind-the-wheel evaluation. This screening should include a complete review of the medical history. Current medications should be reviewed to identify salient problems or to anticipate any issues potentially related to pharmacological agents. Interview should include the individual and any family members or friends who can provide insight.

Following review of the medical records, assessments of vision, physical, cognitive, and psychological components should be performed. Visual screening should include components of the optic system (eye and motility), primary visual system (optic nerve, chiasm, tract, and radiations), and the secondary visual system (visual perception). Within the optic system, assessments include distant and near acuities. Ocular motility is assessed for pursuits, saccades, convergence, and divergence. Refined coordination of the 12 eye muscles is necessary to move the eyes in a rapid, accurate manner to obtain visual information to react to the dynamic environment. Accommodation from distant to near vision and the speed at which a person accommodates is essential. Accommodation speed is necessary as the person is constantly changing focus from distant to near as the driver looks at the odometer and glances at the distance to anticipate the upcoming environment as well as the immediate environment. The accommodation convergence reflex must be rapid and well coordinated. Pupillary responses must be intact for necessary changes to dimly lit areas (e.g., shaded areas or tunnels) and to brightly lit areas. Eye alignment impacts diplopia or may cause blurring, particularly as fatigue increases, and impacts the driver's ability to read signs, perceive depth and distance, and have proper lane positioning.

Visual fields, suppression, and visual neglect must be evaluated. Discriminating between deficits related to visual fields, suppression, and neglect is necessary for predriving therapy, anticipation of problems behind the wheel, and implications for driving training strategies. Deficits in visual fields, binocular vision, or neglect often occur without the driver's awareness, which impacts the driver's ability to obtain information from a visual field. Binocular vision is not necessarily a prerequisite for driving. A driver with a known visual field cut may be trained to scan toward the limited visual field whereas a person who suppresses a visual field may not have been trained to scan into the suppressed area. Suppression may not only affect how much information a driver captures but will also impact accurate depth perception. Visual perception skills must be adequate to properly interpret our environment, particularly from constancy, visual memory, visual closure, and visual discrimination. Accuracy must be coupled with rapid visual

processing speed. Color discrimination and contrast sensitivity are also important in the vision assessment process.

The physical assessment should explore range of motion restrictions throughout lower and upper extremities, trunk, and cervical spine to ensure adequate range to operate the steering wheel, manage foot pedals, and look over the shoulders into the blind spot. Limitations can be accommodated with various modifications ranging from simple to complex. The driver must have adequate strength and endurance for pushing a gas pedal and brake pedal, grasping the steering wheel, and sustained contraction without fatigue. Visual motor coordination must be refined. Coordination of lower and upper extremities for gross movements and rapid fine movements as well as eye–hand–foot coordination should be evaluated. Alertness is a prerequisite for sedentary cognitive and visual tasks and is imperative for driving. Adequate balance reactions and trunk coordination with the visual and proprioceptive system are necessary for steering around corners or cloverleaf configurations on many freeway systems. Vestibular function, in coordination with the visual and proprioceptive system, must be intact in order to provide a proper sense of position, linear acceleration, or deceleration.

The patient's cognitive status must be assessed on several levels. As a foundation to cognition, attention is a prerequisite for further processing and must be intact to drive safely. Attention must also be sustained for protracted lengths of time and shifted and divided between various environmental stimuli, such as an ambulance, as speed is monitored or other occurrences in the car. Cognitive processing speed should be assessed thoroughly, particularly in a visually and auditorily distracting environment as processing speed may slow in a dynamic environment. Basic path finding and topographical orientation should be assessed to project the patient's anticipated skills when behind the wheel. There must also be an assessment of psychosocial, emotional, and behavioral function. This may include frustration tolerance, conflict management, behavior in overstimulating environments, and coping strategies.

Once the assessment is complete, a compilation of overall strengths and weaknesses must be completed and discussed with the primary and ancillary treatment teams. It may be that the patient has areas of weakness but still participates in a driving assessment. Driving skills behind the wheel may be better than anticipated, depending on the driver's prior experience. It may also be an opportunity to educate the driver with poor insight to deficits and the family on the concrete risks of driving and to explore other means of community transportation.

If the patient is cleared to participate in a driving evaluation, a visit to the DMV may be required to obtain a temporary permit. This process may include an interview with a safety officer as well as a written test. Presence of therapy staff is beneficial to advocate on the patient's behalf or to present concerns from the clinical staff. If the driver's license has not been suspended, it is still important for the person to obtain a behind-the-wheel assessment. This assessment team includes an OT and a driving rehabilitation specialist (either an OT specializing in driving or a certified driver specialist).

A typical evaluation should grade intervention from simple to complex environments, such as beginning in residential areas and moving to a congested downtown business district. Begin in a parking lot or isolated area to address basic skills, such as steering control, backing up, using mirrors, managing the controls, and accelerating and decelerating with control. Drive into a residential setting to look at lane position, approach to an uncontrolled intersection, and speed control. Transition to a business district with increased traffic, one-way streets, and greater visual stimuli and distractions. The freeway should be driven to look at control, speed, and merging onto and off of the freeway. The evaluators look for scanning; intersection approaches; good control over the car; appropriate speed, including acceleration and braking; and attention and distractibility, including radio, telephone, and conversation. The occupational therapist and driving rehabilitation specialist should collaborate on the assessment outcomes and make recommendations to the DMV if it is necessary to regain a license, educate the patient, and inform the family. Further driving instruction is often necessary to address weaknesses and to increase the patient's comfort and self-efficacy.

Driving is a reflection of a person's independence, so most people are unwilling to voluntarily relinquish their driver's licenses. It requires a committed staff that the patient trusts to assist remediation of driving skills, protect the patient, and to ensure safety for the community. Given the complexity and dangers of driving, it is an activity of daily living that all providers should consider.

Functioning at heights

Falls are the primary cause of TBI. Whether or not the initial injury was caused by a fall, many people have a fear of returning to heights after injury. However, they may not consider a kitchen stool, chair, or ladder as a risk. It is important to consider impairments related to visual, proprioceptive, and vestibular systems and emotional control. These problematic areas may place the individual at greater risk of falling and exacerbating the existing injury. Repositioning some overhead objects to easily reachable heights reduces the need to use a step stool. Special consideration must be given to those individuals with the potential to return to vocations requiring use of tall A-frame or extension ladders or climbing telephone poles or working on roofs.

A thorough evaluation of balance should be completed. This evaluation includes balance with a narrowed base of support, proprioception, visual perception, balance reactions, coordination, and strength. Components of the evaluation must include issues related to ladder safety involving proper placement, ground surfaces, and harness equipment. The actual height assessment should include graduated levels ranging from small kitchen ladders to 6-foot, A-frame ladders to 15-foot extension ladders. The patient should be

required to carry a small toolbox or occupation-specific objects up and down the ladder, work overhead, and look in all directions. The evaluator should note changes in balance, inaccurate steps, complaints or signs of dizziness, fearfulness, safety judgment, and problem solving.

Despite all of these considerations, it is generally recommended that, following a TBI (even an MTBI), the individual should not be required to work at heights.

MANAGEMENT OF RESIDUAL PHYSICAL DEFICITS

Once the evaluative process has been completed and the treatment team has shared their findings, the individual rehabilitation program begins to take shape. The purpose of treatment is to facilitate relearning and continue the momentum of improvement in skills, thus reducing dependence. The development of a management plan begins with understanding the factors that limit adequate performance. As is evidenced by the complexity of the evaluative process, the management program can be expected to be equally complicated.

Neurological rehabilitation differs from other types of rehabilitation in that people who have sustained neurological damage frequently evidence multiple areas of impairment in addition to those areas that require physical restoration of function. These individuals often cannot be left alone to undertake therapy exercises. They require attention for safety, follow-through, motivation, documentation, and ongoing evaluation. Treatment is best conducted in one-to-one treatment settings. Therapists must possess adequate knowledge of evaluative and treatment techniques and must also possess a repertoire of interpersonal skills that will enable them to motivate the unmotivated, calm the agitated, or educate the person in denial. There will be times when a therapy session is nearly consumed by education or counseling and others in which the session focuses exclusively on prescribed exercises.

The treatment environment should be such that the treatment can be segregated from high stimulus environments that distract the individual if necessary. Attentional deficits that accompany brain injury can make it quite difficult to focus on the treatment session. Overstimulation can lead to behavioral problems.

Rehabilitation of physical function requires maximal repetition for change in the neuronal circuitry. For example, Carey et al. showed that significant cortical reorganization and functional improvement occurred when individuals experiencing poor grasp-and-release as a result of stroke performed more than 100 repetitions of a finger-tracking exercises per day.[93] A different study showed that patients with TBI who received more than 160 additional repetitions of sit-to-stand and step-ups had a larger improvement than those patients who did not receive additional repetitions.[94] In animal studies, structural neurologic changes followed an induced stroke to the hand area in nonhuman primates when the subject performed 400 to 600 reps per day of a fine-motor task.[95–97] It is important that clinicians consider the number of repetitions a person must complete to maximize the adaptive plasticity that leads to greater independence. This information demonstrates that density of treatment and opportunities for challenge extend beyond a therapy session. For example, residential treatment in which a patient is challenged to complete all ADLs, engage in home exercises, and integrate into the community offers environmental challenges.

The therapist should develop the ability to approach treatment exercises hierarchically, utilizing task analysis, when necessary, to break larger tasks into smaller ones to accentuate the learning experience. TBI results in changes in the manner in which a person acquires new information, so physically restorative therapies may be expected to take longer in the neurologically impaired population as contrasted with other populations. To that end, quantitative measurement of treatment exercises that have been broken into smaller, more readily learned components can give a clearer picture of slowly progressing improvement.

Therapeutic measurement

It is now more widely accepted that continued rehabilitation with the traumatically brain-injured person can bring about substantial reduction in disability, improvement in living status, and improvement in occupational status.[98–103] This was not always the case, however. In the time when rehabilitation for this population was largely restricted to the acute rehabilitation experience, it was necessary to develop methods of measurement that would allow both the therapist and the consumer access to critical review of the therapeutic process. Progress could no longer be viewed through the subjectivity of the therapists' eyes; instead, a new period of accountability was emerging. Qualitative summaries of patient performance were no longer acceptable. Many therapists found the expectation for quantitative analysis to be difficult, but once accomplished, the improved objectivity about therapist–patient performance, over time, allowed for some major therapeutic advances. In fact, quantitative measurement allowed therapists to acquire new perspectives about breaking therapeutic tasks into hierarchical components so as to better teach skills to a learning-impaired patient. Therapy became easier to implement and monitor, and patients were better able to benefit from treatment.[10,14]

In order to most accurately understand whether a patient is benefiting from treatment, the therapist must reduce the therapeutic task to its hierarchical components, which can be operationally defined and objectively measured. For example, in evaluating ambulatory skills and progression therein, the therapist should refrain from characterization of skills as follows: "Mr. Smith is able to ambulate short distances with a hemi-cane." Rather, the therapist should characterize Mr. Smith's performance by a statement such as "Mr. Smith is able to walk 100 feet with a hemi-cane in a mean of 2 minutes. This is an improvement from a mean of 3½ minutes for the same distance last week."

Quantification can generally be achieved fairly readily. The therapist can count repetitions of a task, document specific amounts of weight or resistance being used, time performances, and/or count accurate versus inaccurate performances to obtain a percentage correctly performed. Of course, there remains room for subjective observations as well, but therapy that is quantitatively approached is far easier for all parties to participate in, enhancing cooperation, motivation, consistency of treatment, and ultimately, progress.

The therapist should keep in mind that the brain-injured person has a number of special needs. In today's environment of managed care, it is important to keep the therapeutic focus on tasks that will translate, quickly and efficaciously, to good functional improvement. At the same time, the very measurement that is advocated herein may become the data utilized to justify continued treatment toward a longer-term goal of improved functional capability. Outcomes are being viewed, increasingly, from the perspective of financial risks and benefits. Ashley et al.[98] address the idea that rehabilitation outcome translates to dollar savings for long-term care costs. These savings have their beginnings with the daily therapeutic sessions undertaken by the PT, the OT, and their allied health associates. Another study by Spivack et al.[104] demonstrated a clear relationship between treatment intensity and rehabilitative outcome. Thus, in order to advocate best for the TBI person, quantification of treatment will be of critical importance.

During treatment, the therapist must teach other pertinent clinical and residential staff methods that they can use to maximize the individual's learning throughout the entire day. Management of physical injury residuals cannot be performed in a vacuum apart from other therapeutic disciplines or from environments within which the person will be expected to function. Therefore, an important daily goal is to generalize skills into actual activities in residential and community environments.[16,18] This is when environmentally valid learning takes place. Maximized repetition and structure, performed in sequence and in realistic situations, maximizes the derived rehabilitation benefit. Fairly recent findings from Saladin[105] and Ezekiel[106] indicate that infrequent feedback while the patient practices movement exercises is actually more beneficial than constantly given feedback.

Another factor to take into consideration is that the person with TBI is not passively traveling through the rehabilitation process. In physical and psychological terms, therapy is difficult work for the person with TBI. Confronting one's weaknesses is never easy. Early review of the individual's personal history and lifestyle can provide key information to fuel motivation. Perception of purpose and realization of goal achievement are enhanced by the therapist's ability to present concrete, appropriately sequenced tasks within the scope of the individual's interests. Progress requires a constant series of challenges. The therapist must be a creative motivator.

Mobility

Functional mobilization may be influenced by such injury residuals as fractures, peripheral nerve injuries, general weakness, pain, sensory impairments, visual impairments, and balance and coordination deficits as well as cognitive and behavioral factors. Each must be addressed to allow progress to more advanced performance levels. The goal is to facilitate and normalize movement, which will gradually advance into daily mobilization. ROM and adequate strength to move are among the fundamental requirements that can usually be conventionally addressed.

Motor learning occurs when the patient practices a movement and a permanent change in motor performance takes place.[107] Learning a new skill or relearning skills that lead to performance of a task that is meaningful to the patient begins with the simplest component of that task. Each part is learned until the whole is accomplished. It is the hierarchical progression of "simple to the complex." Bobath[1] and Umphred[10] encourage the therapist to bring the patient into the problem-solving process as the task is achieved. As the skill is practiced in meaningful tasks in real-world settings, automatic levels can be achieved. At that point, further refinement of the skill should lead to the ability to carry it over. Advancement in neuroimaging now validates this process by revealing changes in cortical representation (neuroplasticity).

Physical mobility is dependent upon myriad complex movement patterns that meet or surpass environmental demands. Mobility is comprised of patterns that integrate motor output, visual, vestibular, somatosensory input, and cognition.[108] The complex heterogeneity of brain injury mandates clinicians to evaluate a person's deficits comprehensively and efficaciously without compromising either for the sake of expediency. Failure to properly identify direct and contributing impairments may lead the clinician to provide a less effective treatment dose or recommend an inappropriate level of care. Either result may compromise clinical efficiencies and effectiveness. Greater disability, long-term costs, and decreased quality of life may be a result of delayed or limited potential clinical progress.

A comprehensive mobility evaluation must be followed by proper intervention to address direct and related impairments. Deficits in motor control often result in compensatory movements[109,110] and reinforce movement patterns that may prevent the reacquisition of potential movements.[111,112] Inadequate treatment dose, timing, and frequency of the correct intervention may lead to compensatory movements or learned nonuse. Learned nonuse may profoundly limit a person's ability to care for one's self, resulting in greater dependence and limited quality of life as well as long-term personal and societal costs. Learned nonuse may also induce psychological and social problems.[113]

The proper dose of intervention should be coupled with proper environmental demand. Environmental demands provide necessary sensory input and motor output requirements. If the environmental demands are inadequate or a

person is allowed to experience learned nonuse, the person is deprived of necessary sensory inputs and motor outputs required for remodeling pathways. Reduced afferent information is demonstrated in changes in cortical representation.[114] Furthermore, physical movement is constrained by the person's individual characteristics (size, cognition, motivation, etc.) and tasks.[115] Therefore, the evaluation will guide a clinician to identify interconnected components that cause mobility deficits, apply the correct intervention and dose, avoid maladaptive plasticity of compensatory strategies and learned nonuse, and remediate skills that can be generalized to different tasks and environmental demands.

Theories and frameworks guide the clinician to use correct interventions to remediate deficits. Dynamic systems theory is a broad motor control theory that acknowledges mobility as an emergent property as the neuromuscular system and the environment interact.[116,117] Motor control theory is a useful framework that clinicians use to remediate deficits. Motor learning is understood as a sequential process that includes acquisition (initial performance of a new task), retention (attaining the skill following a brief or extended delay), and transfer of skills (use skills to complete a similar but different task).[118] This framework reveals limitations with compensatory strategies because a skill has not been attained or retained. Generalization of skills to new tasks using compensatory strategies may limit further recovery and independence. In addition, skill generalization to new tasks cannot be expected with an abbreviated or inadequate dose of treatment, and skill retention during extended delays is not achieved.

Motor learning may be constrained by concomitant cognitive impairments. Explicit and implicit learning or trial-and-error and errorless learning, respectively, are involved in motor learning. Implicit learning has been demonstrated in cognitive remediation[119–121] and with other neurological conditions,[122] but it is not as well researched as it relates to motor learning. Growing evidence shows the efficacy of implicit motor learning, particularly when the injured person has cognitive impairments. An individual with cognitive impairments may have a predisposition to rely on explicit knowledge of movement, which causes errors and disrupts optimal performance.[120,121,123] Implicit learning applied to movement impairments can be undertaken as the clinician progressively gradates activity from a very easy condition, with which success is highly likely and errors are minimized, to more difficult conditions. Aside from grading the activity, the clinician can also use facilitation treatment approaches based in motor control theories to minimize errors.

Motor control theories and treatment approaches, such as NDT, support a clinician's attempt to improve and normalize movement. Motor control theory and NDT overlap and work in conjunction rather than conflict. The Bobath approach, or NDT, is currently defined as a problem-solving approach to the assessment and treatment of an individual with disturbances of function, movement, and postural control due to a lesion of the central nervous system.[112,113] In other words, the clinician must understand that interaction between the person's skill components and the environment. The treatment approach contends that building physical stability with correct postural orientation is essential for proper mobility. Movement strategies will be determined by a person's postural orientation relative to the base of support and gravity.[124,125] The environment demands constant and concomitant exchange between stability and mobility.

Although a clinician understands the exchange between the patient's stability and mobility with the environment, it is also critical to consider and understand the interplay between closed and open kinematic chains.[126] The upper extremity mostly functions in an open kinematic chain in which the hand moves freely and more dynamically compared to a closed kinematic chain. An example of an open kinematic chain movement is bringing a cup toward your mouth or reaching into a cabinet to get objects. If proximal structures of the upper extremity are not used as stabilizing structures, then distal segments have a higher degree of inaccuracy. In contrast, closed kinematic chains recruit muscle and joints acting within the kinematic chain, such as transferring from sit to stand or pushing one's self up from the floor. Movements in one joint will produce predictable movements in all other joints along the closed chain. For example, transfers from sit-to-stand recruit cocontraction of muscles at the foot, ankle, knee, and hip.

Clinicians should provide appropriate sensory feedback as needed. Facilitation should be regulated on the basis of timing, modality, intensity, and withdrawal.[108] Clinicians not only need to make sure the implicit learning is optimized through the task demands but through facilitation as well. Hesse[127] demonstrated improvement in spatial and temporal parameters and patterns of muscle activation during facilitation. Miyai et al. showed similar changes as well as changes in cortical activation in the affected cerebral hemisphere.[128] Clinicians have the opportunity to use afferent input in Bobath approaches to reeducate the person's movement efficiency and effectiveness.

Abnormal tone/spasticity

The problem of abnormal tone has been addressed in a variety of approaches. Most rehabilitation physicians recognize that the sedating properties of antispasticity medications can further handicap the patient. Alternatives include stretching exercises, such as proprioceptive neuromuscular facilitation,[5] and local injections if just one or two limbs are involved. The patient with severe global spasticity, such as quadriplegia caused by a brain stem lesion, continues to be addressed with an intrathecal Baclofen pump. A preliminary evaluation by the physiatrist is necessary to determine if the pump will be an appropriate choice for the patient.

Other approaches to address dysfunctional mobility, caused by abnormal tone, is the NDT/Bobath approach.[1] The early Bobath approach evolved as it was realized that the earlier interventions, once believed to have been "automatically carried over into functional performance," did not always

work (p. 400).[129] Earlier beliefs about inhibiting abnormal tone with "reflex inhibiting postures," later, "reflex inhibiting patterns," was changed to the current approach that gives more focus on movement and function by having the patient take a more active role in treatment. Bobaths' techniques normalize movement patterns, through inhibitation, facilitation, and stimulation, to provide the foundation for functional activity, which is then carried over by working in the functional activity.[130] The patient's ability to interact with the world surrounding him or her involves the ability to "plastically adapt and learn from new challenges." This allows the patient to fine-tune motor responses.

In 2007, Mayston[131] listed aspects of the Bobath concept that have remained consistent:

1. Problem-solving and analytical approach in assessing the patient.
2. Therapists must be knowledgeable of tone, patterns of movement, and postural control underlying performance of functional tasks.
3. Handling and activation techniques can be used to modify the way a task is performed. This process makes achievement of the skill more efficient, effective, and successful for the patient.
4. The patient is encouraged to be an active participant.
5. Application of movement, including practice, is important in achieving function.

Mayston's list of aspects of the Bobath concept that have changed include the following:

1. Past understanding of tone has changed to encompass both neural and non-neural.
2. Past belief that spasticity was the major source of the patient's movement disorder has changed since Lance's[38] definition recognized that spasticity is rarely the major cause.
3. Past dogmatic teaching against incorporation of other modalities with the Bobath approach has changed and is now open to use of other modalities that complement the Concept's treatment. These include use of the treadmill, structured practice, and use of orthotics and muscle strengthening. (It was once believed that muscle strengthening would cause an increase in spasticity. Research debunked that belief.)

Research on NDT prior to 2000 found that the technique was "outdated." However, research conducted since recent revisions has shown that the technique demonstrates positive changes in gross motor performance.[132,133] As would be expected, further research is encouraged.

An emerging gait training strategy uses the concept of partial body weight support (BWS). The individual is secured in a harness, which provides 0% to 50% of support of body weight. The system may be used on a level ground surface or suspended over a treadmill. The harness system eliminates risk of falling, and the person is able to gradually accept an increasing amount of his or her own body weight during standing and/or ambulation. With no fall risk, gait training can begin earlier in the rehabilitation process.[134–137] Also, the therapist's hands are free to facilitate normal movement while the person is in the upright position. A critical component in this treatment technique is the physical cues provided by a therapist. These cues include weight shifting, stabilizing the trunk, rotating the pelvis, advancing the affected limb, and so on. Use of the BWS technique during gait training in hemiplegia produced better results in regard to functional balance, motor recovery, walking speed, and endurance as compared to gait training with full body weight. Research has shown that ambulation was improved with partial weight-bearing protocol, including reduced stance time on the unaffected limb, increased weight acceptance on the affected limb, increased gait velocity, and improved gait symmetry.[135,136]

Studies of people with spinal cord injury have shown that, when provided with the proprioceptive input of weight-bearing during gait, the lumbosacral spinal cord can generate rhythmic locomotor EMG patterns even in the absence of supraspinal influences.[137] This indicates that control of the flexion/extension pattern of walking is in the spinal cord, and in the case of damage to the brain, these central program generators can be activated to facilitate and improve ambulation. Research on gait training with body weight support system in the TBI population is extremely limited and is an area in need of further attention.

Treatment of mobility skills is greatly enhanced by daily practice of these skills in the residential setting. Bed mobility can be practiced every day in the environmentally valid routines of getting up and going to bed. Trained staff should be present to assist in additional home exercises that should be designed by the clinical staff to ensure the use of proper techniques. The same is applied to all transfers, toileting, bathing, and early ambulatory routines. The individual advances through these daily routines from the clinic to the residence to the community until greater independence is accomplished.

Helpful resources for the neurologic PT and OT include the following:

1. Umphred's *Neurological Rehabilitation*, 6th edition, Mosby (Elsevier) (2013)
2. Anne Shumway-Cook, PhD, PT and Marjorie H. Woolacott, PhD. *Motor Control: Translating Research into Clinical Practice*, 4th edition (2011), Williams &Wilkins
3. *The Bobath Concept: Theory and Clinical Practice in Neurological Rehabilitation*, 1st edition. (2009) Authored by members of the British Bobath Tutors Association located in England. Blackwell Publishing, Ltd.

Pain

In management of pain, it is very important to utilize a system that allows for the person to rate the pain experience throughout the day. A pain diary provides a way to

document and rate pain. A rating scale of 0 to 10 (0 = none and 10 = most severe) is a simple scale for the person to use. Headaches or neck and back pain in the brain-injured person can become a distracting somatic focus, and perseveration on pain may hinder progress in several aspects of the TBI program. An assumption that pain is exaggerated should not be made until complaints of pain are explored to rule out potential causes that may respond to treatment.

It is important to keep a concomitant recording of the degree to which pain impacts the person's ability to function. These reference points can be utilized by the treating physician and team to determine appropriate medication and therapeutic approaches. The physician must review all medications taken by the patient and determine what modifications, if any, should be made. Dosage and frequency of medication taken should be included in a diary. The physician may elect to utilize a controlled reduction of dosages with combined pain medications. Consultation with an experienced pain management physician may be required in some cases.

The therapist will have a major impact upon the individual's understanding of the various causes of pain. The individual who anticipates pain from movement develops increased anxiety and muscle tension and, therefore, the potential for chronic pain and stiffness. A kinesiological orientation in the initial exercise program may be an effective tool to reduce this anxiety-produced pain and allow the patient to begin to move through and beyond pain. This approach teaches normalizing posture and improving body mechanics with more efficient movements to reduce pain.

Conventional therapeutic modalities include thermal treatment, ultrasound, transcutaneous electrical nerve stimulation (TENS), massage, aquatic therapy, flexibility exercises, and strengthening exercises. Pain management is best enhanced by involvement of psychological services for the individual to explore relaxation or hypnosis as potential avenues of treatment. The best approach to pain management is to address all deficit areas while unifying the physician, the treating therapist, and treating psychological team.

Postural control and balance

Fisher[44] describes postural deficits commonly seen in people with TBI and contrasts their postural abilities to normals. In general, the individual with TBI can be observed to tend toward the relaxed sitting posture of normals, however, on a habitual basis. Trunk movements do not tend to be incorporated into arm movements, and even when attempting to assume an erect sitting posture, truncal musculature strength and coordination may make achieving the erect position quite difficult. Not only do truncal weaknesses impact upper extremity function, but transfers can also be impacted. In preparation for arising from sitting to standing, postural deficits frequently will maintain weight so far posteriorly as to make the attempt to arise ineffective.

Effective treatment of postural deficits focuses on strengthening of the truncal musculature. In cases in which there is concomitant cerebellar dysfunction, strengthening may not be indicated so much as learning selective utilization of muscle groups with slow, controlled muscle activation. In cases, however, in which a cerebellar component is not present, strengthening exercises, such as bridging, sit-ups or crunches or resistive lateral bending, can be helpful. It is important to achieve stabilization at the hips, back, neck, and shoulders. Activities such as hippotherapy and therapeutic horseback riding are also excellent ways to retrain the postural system and can impact balance along with visual, psychological, and vestibular enhancement.

Cerebellar dysfunction

Stroke, tumor, degenerative disease, and trauma are possible causes of cerebellar ataxia. Damage may have occurred to the structure or to the pathways leading to and from the cerebellum. These may be motor pathways or nonmotor pathways. The primary dysfunction typically addressed by the PT and OT is poor coordination of movement or ataxia often without muscle weakness. Cerebellar tremor is an "intention" tremor that is differentiated from the "resting" tremor seen in patients with Parkinson's disease. Intention tremor occurs when the patient attempts to perform movements, such as reaching for a glass of water.

Many therapists struggle with movement disorders related to cerebellar dysfunction. Frustrations with ataxia or tremors in the extremities and/or trunk are compounded by the short period allowed for treatment and often lead a therapist to teach compensatory techniques (i.e., using the more functional limb or mobilizing from a wheelchair). Minimal to no time is then spent in therapeutic confrontation of the issue. Medical management with pharmacological agents have been used with little success. This leaves the patient with physical rehabilitation as the most helpful approach to attempt to decrease symptoms or regain any functional control. If the dysfunction is caused by a degenerative disorder, physical therapy is usually unsuccessful. Morton and Bastian[10] provide informative detail regarding the cerebellar dysfunction and potential avenues for rehabilitating lost functions. They have indicated that "evidence for the effectiveness of treatment for patients with primary cerebellar damage" involving ataxia has been quite limited and incomplete. During the initial evaluation process, the therapist will need to determine if improvement with intervention is expected or not. This is true in the case of cerebellar damage caused by progressive disease with which progress may not occur. If the expectation is that intervention could help, a trial-and-error approach may be taken to challenge motor functions. This would include areas of balance and gait skills. If recovery is not expected, compensatory strategies may help to at least stabilize functions.

The use of weighted vests or packs or weighting individual limbs has been a trend with some therapists. The hoped for result is that movement will become smooth and tremor reduced. However, the benefit of this approach usually does not continue when the weighting is removed. In fact,

weights added to distal segments of the limb can result in an increased amount of hypermetria (past-pointing) when simple single-joint wrist activity is attempted.

The decision to pursue rehabilitation of cerebellar-related deficits may depend upon funding that will allow the time for this intensive and necessary effort. The rehabilitative program includes learning to relax selective muscle groups on command to reduce the excursion of tremor. The individual must learn to selectively "turn on" one muscle while maintaining relative electrical silence in the antagonistic muscle. EMG/biofeedback training may be helpful in teaching the patient to control muscles.

If postural tremors are severe, it may be helpful to begin treatment to stabilize the trunk, head, and neck with the patient in the supine position. To establish a stable base of support, the performance of any task requiring an ataxic extremity to extend away from the body requires trunk stabilization. Therefore, goals of treatment are postural stability and accuracy in extremity movement during functional activities. Treatment must be pursued in a sequential manner until the individual is independent in each component—that is to say, head and trunk control must be addressed and established prior to sitting or ambulatory activities. If poor head control is evident, initiate treatment with prone-on-elbows positioning or seated at a table, feet firmly planted on the floor, with weight on the forearms. If there is poor trunk control, bolsters, wedges, or pillows will assist with support in the prone position. The neck extensors can be briefly brushed with ice, no more than 5 seconds, followed by a stretch and then heavy resistance to the extensors. This is followed by downward compression on the shoulders. The goal is to maintain the head in a steady upright position. Progression to management of trunk control will require a graduated removal of the pillow supports, and an increased demand will be placed on the elbows and shoulders. Approximation through the shoulders should be provided. Weight shifting should be practiced until the individual is able to sustain support on one elbow. Additional mat activities can include the quadruped position combined with joint approximation through the shoulders and hips and weight shifting. During this phase, trunk rolling and supine/prone-to-sit exercises can be practiced with graduated mild resistance given by the therapist. The person should progress to crawling activity to challenge balance, strength, and weight shifts in reciprocal patterns.

As head and trunk control improve, sitting can then be addressed. Sitting on surfaces without benefit of structural supports (i.e., the edge of a mat or chairs without arms or backs) should be used. Stabilization is promoted by joint approximation at the hips and shoulders. Weight shifting should be practiced. Another mat activity can include the tall-kneel position. The therapist should provide approximation through the shoulders and hips, and weight shifting can be practiced. Contact support can be initially provided by the therapist. As stabilization and balance improve, support is gradually reduced.

During progress in sitting and tall-kneel activities, the upper extremities should be extended from the body to challenge trunk stability. Head and trunk rotations and bending from the hips can be practiced with one or both arms extended overhead, laterally, or forward. Realistic movements should be practiced (i.e., reaching for objects overhead, to the side, or from the floor). Functional upper extremity activities may be practiced while sitting or tall kneeling at a table. To progress stabilization, weight may be shifted from one forearm to the other while the opposing extremity is active. This support is gradually reduced until two-hand activities can be practiced. Mild resistance to the trunk and extremities for feedback is initially helpful to the patient during movements. This can be provided manually by the therapist or by light wrist weights.

As head and trunk stabilization improves in sitting, supine/prone-to-sit, and tall kneeling, the individual should practice transfers. Initiate transfers from the most stable position (i.e., sliding surface to surface) and graduate in degrees of difficulty until the person is safely independent.

Much of the above activity prepares the person for standing and ambulation. Rolling, assuming and maintaining the quadruped position, crawling, and tall kneeling are the basic neurodevelopmental sequence positions necessary prior to standing. Overall strengths, endurance, and balance must be adequate to launch into the demands of the upright position. The person should repeatedly practice moving through foot placement, sliding forward, flexing from the hips, and pushing upward with a sense of center of gravity and balance. Manual guidance from the therapist and visual feedback from a mirror can initially assist the individual as extension of the hips and knees move the individual to the upright position.

Once stability in standing is accomplished, the ambulatory phase can be initiated. A front-wheeled walker may be the first support device required for ambulation practice. On occasion, weighted walker legs may be necessary to assist stabilization. If appropriate, tall poles can be quite effective in developing a sense of rhythm, pace, and reciprocal movement.[138]

Past-pointing or dysmetria will benefit from various techniques, such as biofeedback, PNF,[5] and Frenkel's exercises. Aquatic or pool exercises may be beneficial for relaxation of the person with ataxia.

Diminished ability with rapid, alternating movements, dysmetria, hypotonicity, and/or movement decomposition are manifestations of cerebellar damage that influence performance in ADLs (i.e., feeding, brushing teeth, dressing, or gait functions). OTs have begun to use a product from gaming consoles to assist patients during practice of functional movements required in food preparation. The Wii™ (www.wii.com) product has a virtual reality program that allows a person to practice such movements as chopping or cutting foods without using a real knife. Movements are practiced until the patient has reached a safe level of movement control to begin using a real knife. The therapist monitors transition into the patient's home kitchen as the

desired level of independence is realized. Reading or other skills that require accuracy in visual scanning ability can be impacted by oculomotor deficits related to cerebellar injury. A spastic hemiparesis may further complicate an ipsilateral or bilateral ataxia in one or more limbs. Acquiring a degree of movement control and normalizing functions can be frustrating.

Sensory function

An intensive effort should be made to stimulate sensory functions to normalize tactile sensitivity.[49,71] Keenan and Perry[139] noted that the sensory functions necessary for hand function included awareness of pain, light touch, temperature, proprioception, and two-point discrimination of less than 10 mm. Yekutiel and Guttman[140] documented that somatosensory deficits in the plegic hand can significantly improve with intensive sensory retraining that incorporates functional tasks. The performance of basic self-care skills requires an integration of perceptual, cognitive, sensory, and motor functions. The ability to perform a motor task will depend upon the interactions of the residual components that are functioning throughout these systems.

Assessments will determine the specific deficits to be addressed. Treatment requires adequate time and opportunities to maximize repetition of stimuli. Also, incorporate visual input into treatment sessions to increase awareness.

If a significant motor impairment accompanies the sensory deficit, improvement of the motor function is usually addressed first. Tactile stimulation, however, can and should be incorporated into the initial treatment sessions. Weight bearing on the impaired extremity, through the palmar surface, on a variety of textured surfaces (i.e., carpet, sand, or smooth metal) will facilitate motor function, proprioception, and touch. As improvement occurs in motor and sensory functions, progress to functional two-handed tasks. These tasks may include weight bearing on dirt or sand while gardening, holding down paper while writing, or weight bearing on the extremity while eating with the functional extremity.

Deficits in touch are addressed by providing a strong stimulus to the extremity. Initial sessions open with stimulation via rubbing various textures over the extremity. If possible, have the individual actively move the textured material over his or her own extremity with the unimpaired hand. Make the person aware of any abnormal positions in the extremity or hand during activities. This should be immediately corrected to stimulate a sense of normal touch during movements. Functional tasks in repetitive daily routines can include washing, rinsing, and drying the hands; dusting; cleaning windows; making the bed; or folding laundry.

Individuals who have hypersensitivity or sensory defensiveness may be appropriate for sensory integration techniques, such as the Willbarger Protocol.[141] The protocol involves establishing a set sensory routine that encompasses deep proprioceptive input with active physical proprioceptive activity. Special training courses are offered to learn and teach the technique.

Hemiparetic limb and CIMT

The loss of sensory and/or motor function to an upper or lower extremity handicaps the patient in ways that are frustrating. The patient resorts to exclusive use of the intact limb at the exclusion of the impaired limb. Taub called this behavior "learned nonuse" (LNU).[142] Taub theorized that LNU could be reversed by "forcing" use of the impaired extremity. He surgically abolished (deafferentated) neural pathways providing sensory (somatosensory) feedback to the forelimb of primates. The motor nerves were spared, which allowed the potential for motor function. After attempting to use the impaired limb led to frustration, the primates resorted to exclusive use of the intact limb. Dr. Taub then "constrained" the intact limb and observed the primates initiate use of the impaired limb. He then removed the constraint but found that the primates quickly returned to exclusive use of the intact limb. The premature removal of the constraint had not allowed time for the impaired limb to gain strength. In a subsequent study, the constraint remained on for several days, and the impaired limb was used and gained strength. When the constraint was removed, the LNU had been reversed and remained so after 1 year. This was the birth of constraint-induced movement therapy (CIMT).

Studies in humans with limbs affected by stroke and TBI noted significant changes in several motor tasks with LNU remaining reversed after 1 year. In addition, evidence of cortical reorganization or neuroplasticity during and after CIMT has further substantiated that this therapeutic approach is a major advance in treatment for patients with upper or lower extremity motor impairment after damage to the central nervous system.[143]

In 2006, Wolf and colleagues published findings on CMIT from the EXCITE trial, one of the largest randomized multicenter trials and the largest trial of CIMT to that time. In brief, after 3 to 9 months of having a first stroke, the effects of CIMT were "statistically significant and clinically relevant" (p. 2095)[144] for improvements in motor function of a paretic upper extremity following a 2-week intervention period. The effect persisted for up to 1 year and was not influenced by age, sex, or initial level of the impaired limb function. Taub has encouraged additional studies to look at central nervous system changes after use of CIMT.[142]

The original CIMT protocol has been modified over time and has also been expanded to include treatment for aphasia and children. Extensive training formats are available to adapt to specifics of the patient's needs. The variations in CIMT protocols and the accompanying Wolf Motor Functional Test (WMFT) and the Motor Activity Log (MAL) can be found at http://www.uab.edu/citherapy.

Proprioceptive deficits should be addressed while performing motor functions.[145] The impaired extremity is initially guided by the therapist. This progresses to the individual moving the impaired extremity through tasks with

his or her own unimpaired extremity. If grip and strength are available, two-handed activities should then be incorporated to include lifting and movement of various objects (i.e., cans, plastic bottles, a brush, etc.). Engage in activities that include resistance (i.e., sanding or pushing objects). ADL tasks offer numerous opportunities to maximize therapeutic input for proprioceptive impairments. For example, dressing with a proprioceptively impaired upper extremity should begin with the practice of moving the extremity through sleeves or tubular materials. Have the person guide the extremity with the unimpaired hand and emphasize visual input as a reference. Progress to functional activities, such as dressing. Practice should initiate with tasks in front of the body and overhead with visual input. As sensory function improves, progress to tasks without visual reference (i.e., tucking in a shirt, reaching for a wallet behind the back, or reaching for objects under a table).

Smell and taste

In cases in which impairment of smell or taste is irreversible, the individual and family need to be made aware of social, dietary, and safety implications of impaired smell and taste. The person with TBI who will be living and/or working independently in the community will require training in management of perishable foods and toxic materials. Food preparation training must include visual monitoring of food while cooking and identification of altered seasoning practices that may not be healthy. Structure should be established to assist by labeling and dating perishable foods. Pet care, if applicable, should be undertaken systematically. Toxic materials should be moved to a safe place and labeled. Smoke, carbon monoxide, and gas detectors within the home should be utilized and can be assisted by current electronic detection technology.[63]

The workplace must, likewise, be considered when treating for olfactory or gustatory deficits. Education of the employer and coworkers may allow the candidate for vocational placement a chance for return to work with reduced risk. The vocational rehabilitation counselor should take these types of deficits into consideration while looking or planning for vocational placement.

Visual perception and perceptual motor functions

Areas frequently requiring therapeutic intervention are visual inattention, gross ocular deficits, scanning, figure–ground, visuospatial perception, visual memory, and visual–motor skills.

Appropriately trained rehabilitation assistants can augment the clinical program by undertaking home exercises as well as through functional application. Visual perception deficits, such as figure–ground, can be practiced via homework with worksheets and home exercises, such as word searches or community scans. It may be helpful to teach organizational skills and energy conservation techniques to help compensate for residual deficits. Puzzles, form boards, parquetry blocks, and other appropriate games can keep the patient's interest while being therapeutic. Visual scanning while reading or working word puzzles may be useful. Data should be collected and reviewed over time for progress.

Neistadt[145] has indicated that there is an association between functional and constructional skills. The presence of constructional apraxia and visuoconstructive disorders has been shown to impact independent living by difficulties with meal preparation, dressing, changing a tire, or assembling an object. Bouska, Kauffman, and Marcus[65] discuss the importance of teaching the individual to approach a visuoconstructive task via sequential planning. For example, the task should begin first by visually and physically organizing the parts, followed by construction of the object. The person with apraxia benefits from physical guidance to initiate and carry out a simple task. With intense repetition, the ability to wash, groom, and feed should normalize. On higher levels, dyspraxia requires the same touch and guidance to accomplish more complex activities requiring the ability to plan, arrange, and build.

The neurodevelopmental approach to improving perceptual motor skills has been found to be effective and provides a guideline for the progression of treatment as the individual advances. Intensive practice is vital and should be pursued with functionally meaningful tasks in normal living environments.

For additional therapeutic approaches to visual impairments, the reader is referred to the chapter in this text by Suter.

Driving

Independence, in terms of driving skills, can be enhanced through visual therapy and perceptual training.[76] Exercises to address visual attention and scanning, visuospatial relationships, oculomotor skills, eye–hand–foot coordination, and response times are some of the components required to safely drive a vehicle. As mentioned earlier in the evaluation of skills required for driving, retraining should include behind-the-wheel time with a professionally trained driving instructor in a dual-equipped vehicle.

Computer programs to address perceptual skills have become quite popular over the past decade. Many rehabilitation programs have depended heavily upon this tool as a therapeutic base. Although computer-assisted therapy is a useful and motivating approach, it does not provide stimulus to or require responses from other systems (e.g., vestibular, motor, or other perceptual responses).[65] Any dysfunction in the perceptual realm may be impacted by concomitant vestibular and/or cerebellar deficits.[48] Again, the importance of hands-on therapy to reintegrate multiple systems into efficiently coordinated responses requires more than one evaluative or therapeutic approach. If driving skills are not adequate at evaluation, it may well be possible to enhance skills via training. It may be necessary to undertake

drivers' retraining with both classroom and behind-the-wheel instruction in order to improve driving skills.

All therapeutic disciplines should be polled as to potential limitations that may be experienced prior to the driving evaluation. This information should be reviewed by the treating physician and a determination made about the propriety of the driving evaluation. This information will be invaluable to the driving evaluator as the assessment is undertaken.

Cardiovascular fitness

As major sensorimotor deficits are improved and general mobility advances to higher levels, it may be appropriate to initiate an aerobic and conditioning program. These programs can be developed to fit into the person's lifestyle by gradually transferring the exercise routine from the clinical setting to a community gym. The initial exercises must be performed with the therapist's close supervision and medical clearance.

An aerobic and conditioning program can be created for individuals with and without significant motor impairments. Stretching should also be taught to start any exercise routine. An exercise program can be developed with stationary bicycles (standard or recumbent), treadmills, and weights. Muscle conditioning may utilize isometric exercise or full-range exercise with weights, elastic exercise bands, free weights, or exercise machines. Low-impact aerobic exercise routines can be developed with walking, swimming, bicycling, and aerobic classes.

As the person becomes more independent and community reentry is developed, the therapist may assist in the choice of and transfer to a community-type exercise routine (i.e., a local gym or fitness center). Independent aerobic exercise routines can be established in walking, swimming, or bicycling as well as a maintenance stretching and muscle toning exercise program (i.e., sit-ups, push-ups, etc.). Many physical therapists are incorporating yoga stretching techniques and "short form" Tai Chi into treatment sessions. These techniques also provide an additional benefit from balance exercises and various forms of breathing exercises for relaxation.

As the benefits of conditioning renew the individual's sense of well-being and enhance overall functional status, the continuation of exercise as an enjoyable routine may allow a gradual reduction of supervision.

Motorically and cognitively impaired individuals also gain great benefit from a fitness program. Aside from endurance and stamina, it has been demonstrated that thinking ability and emotional status improve with physical fitness.[146,147] As a result, there are enhanced levels of energy, feelings of well-being, and independence for most people with TBI.

Leisure

The intent of the postacute neurorehabilitation setting is to provide an environment in which the individual is assisted in regaining a normal rhythm of living. Although the clinical aspects of the treatment program focus on rehabilitating specific skills impaired from injury, skills are practiced in real-time ADLs. Each time the patient engages in a treatment session, one comes face to face with one's disability, and the intensity of this bombardment can be overwhelming. Consequently, we must not forget the role that leisure plays in rebuilding a new life path. Many patients with brain injury have lost the ability to plan and initiate socialization or have fun. The patient with a significant motor impairment may feel that he or she is no longer able to participate in any type of leisure activities requiring physical skills. However, the creative therapist is able to find activities that will challenge deficits while the patient is having fun.

Although community outings are usually designed to be therapeutic, a sense of enjoyment should be the reward from doing the task. There are many creative tools available for therapists to rehabilitate leisure skills for their patients with brain injury. A leisure outing can range from going to the movies, casual shopping, parks, and museums to playing a variety of games. Music is a potent tool to engage the patient in movement. The virtual reality products of gaming consoles engage not only in motor activities but challenge cognitive skills. Games include such activities as virtual bowling, golf, baseball, yoga, balance, skiing, and tennis. Recent versions involve playing virtual musical instruments. A Wii™ activity can be enjoyed individually or in a group, which engages the patient in a social situation.

Kleiber et al.[148] considered the role of leisure in coping with and adjusting to disability after brain injury in postacute neurorehabilitation settings. Leisure activities are distractions from a daily focus on the negative aspects of disability. A "generation of optimism" helps to break from continual emotional pain after disability. The view is changed, and the "emotional uplift provides the cognitive space for positive reappraisal" (p. 323).[149] Some sense of self is restored. Cheryl Mattingly, an OT and medical anthropologist, created a term for the clinician's role in assisting patients to reconstruct their life story, their identity: "therapeutic emplotment."[150] Pieper[151] put it well by stating that leisure is "an attitude of non-activity, of inward calm, of silence; it means not being 'busy' but letting things happen.…Leisure is not the attitude of mind of those who actively intervene, but of those who are open to everything…of those who leave the reins loose and who are free and easy themselves" (p. 52).

Pool/aquatic therapy

Although the healing elements of water have been used for centuries, organized therapeutic protocols for the neurologically impaired have emerged only during the past decade. Current programs for musculoskeletal injuries (e.g., neck and back) are widely accepted by therapists and well received by those being treated. In this regard, the use of a pool program is a positive aspect to the physical rehabilitation for the person with MTBI. Aquatic therapy can address difficulties with balance and coordination, muscle weakness,

poor endurance, and sensory dysfunctions. The buoyancy and warmth of the water, together with use of appliances to introduce resistive exercises, make a good combination for therapeutic application. Subtle vestibular impairments may manifest in aquatic activities as water reduces proprioceptive feedback, making balance functions more dependent upon visual and vestibular feedback. Precautions for cardiac or other medical considerations should be taken prior to introduction of an aquatic program.

The more motorically impaired person can have quite positive responses to a pool program. Abnormal muscle tone, motor control, gait patterns, and range-of-motion deficits can be addressed by utilizing the characteristics of water. This approach can add an element of fun and should be relaxing. As usual, normal precautions must be taken for cardiac, incontinence, and swallowing issues.[152,153]

SUMMARY

This chapter reviews some of the more recent changes in neurorehabilitation as it pertains to the neurologic PT and OT. The chapter provides a comprehensive review of evaluative and management protocols in areas that are most commonly observed to be problematic on a long-term basis for the person with TBI. The reader is encouraged to adopt an expectation for continued improvement associated with continued treatment beyond acute hospitalization. Neurologic PTs and OTs should understand the tremendously complicated clinical presentation often associated with TBI and become familiar with the ever-evolving treatment strategies that can be used either individually or in tandem to treat the physical residuals associated with TBI.

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Undertaking vocational rehabilitation in TBI rehabilitation

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INTRODUCTION

Return to work (RTW) following a traumatic brain injury (TBI) represents a pinnacle achievement for both the injured individual and those professionals working with the individual. The United Nations General Assembly produced "The Standard Rules on the Equalization of Opportunities for People with Disabilities" in 1993.[1] This report consists of 22 rules that are intended to serve as a guide in policy making for member states. Rule 2 states, "States should ensure the provision of effective medical care to persons with disabilities." Rule 3 indicates, "States should ensure the provision of rehabilitation services to persons with disabilities in order for them to reach and sustain their optimal level of independence and functioning." Finally, Rule 7 states, "States should recognize the principle that persons with disabilities must be empowered to exercise their human rights, particularly in the field of employment. In both rural and urban areas, they must have equal opportunities for gainful employment in the labour market."

Taken together, the United Nations member states call for states to ensure that maximal disability reduction is achieved through access to medical treatment and rehabilitation culminating in gainful employment whenever feasible.[1]

Work is highly linked to identity and has significant meaning for most people, and the value of work to people with TBI is readily apparent to them after injury.[2] The meaning of work after TBI often changes, however, and can have a unique impact on quality of life.[3] Work provides structure to daily routines and provides purpose. The social aspect of work allows for community participation and provides opportunities for building relationships. Work can be a means of returning to a "normal" life and is perceived as a strong and effective means of rehabilitation. Essentially, the ultimate measure of rehabilitative success is life satisfaction; vocational success bears significantly on its achievement. In a study evaluating contribution to overall life satisfaction, individuals with moderate-to-severe TBI reported significantly less satisfaction years after injury with vocation in comparison to an uninjured reference population.[4] Self-directed vocational participation as an adult is promoted from a very early age through young adulthood as a means of securing social and financial stability. TBI frequently deprives an individual of the ability to participate meaningfully in life through vocational and social involvement in keeping with the rest of society.

Melamed, Groswasser, and Stern reviewed gratification of basic needs, physical well-being, emotional security, and family, social, economic, and vocational needs 1 to 2 years following discharge from rehabilitation for 78 people with

TBI.[5] Those individuals who were employed in the open labor market, lived active lives, and had higher degrees of acceptance of disability reported the highest satisfaction. Lower satisfaction was associated with unemployment and employment in protected conditions and with passive, uninvolved lifestyles. These findings are supported by other authors who report life satisfaction associated with employment and degree of social integration.[6,7] Heinemann et al. completed a survey designed to measure the unmet needs of persons with TBI. Responses from 895 respondents indicated that two of the three greatest needs—improving memory or problem-solving skills (51.9%), increasing income (50.5%), and improving job skills (46.3%)—were vocationally related.[8]

Ironically, although rehabilitation endeavors to assist individuals to achieve maximal recovery so that they will have the opportunity to participate fully in life, a societal predisposition exists toward insufficient effort in returning people to the workforce. This is manifest by restricted vocational rehabilitation (VR) benefits under various workers' compensation statutes across the United States[9] as well as by lack of provision of benefits for VR services in any accident and health insurance coverage. VR services provided by publicly funded sources, such as state departments of VR, are often ill-prepared to deal with the complexity of problems presented by persons with TBI.[10–12]

The General Accounting Office (GAO) of the United States reviewed differences in RTW strategies comparing the United States to Germany and Sweden.[13] Public expenditures for VR were two times higher in Germany and 2.6 times higher in Sweden as a percentage of gross domestic product. The GAO cited conflict created by divergent goals of Social Security's eligibility and provision of benefits and VR agencies, resulting often in systematic financial disincentives to RTW. It was concluded that differences also existed in the availability of VR services, timing of vocational referral (later in the United States), and level of financial incentive involved in RTW.

VR services have been available since the 1970s[14] with funding provided by the public sector in the form of state departments of VR or the private sector as a benefit under workers' compensation. The primary thrust of VR (i.e., returning an individual to work) is accomplished by careful evaluation of work responsibilities and comparison of the physical requirements of those responsibilities to the individual's capabilities following injury. Very few conditions present the complexity of deficits seen with TBI, however. People with TBI present with far more complicated problems, including behavioral, cognitive, communicative, psychological, emotional, social, and physical disabilities. The success of VR, therefore, is highly dependent upon the degree of disability present in the individual. To the extent that medical rehabilitation has been truncated, individuals are left with higher levels of disability and with little recourse for additional medical rehabilitation services. As rehabilitation hospital lengths of stay continue to decline and as access to postacute rehabilitation is increasingly restricted,[15,16] fewer people will receive adequate medical rehabilitation to maximize disability reduction and to ready an individual for VR. A small study of 10 individuals reporting self-perceived health care needs and delivery of health care services 5 years after moderate-to-severe TBI found the most reported needs were in the domains of emotional, vocational, and cognitive function.[17] Improving job skills and finding work were cited most frequently.

Provision of VR services is not uniformly applied to all individuals who sustain TBI.[18,19] RTW following TBI is difficult for many individuals regardless of the level of severity of injury[18,20] and is made more difficult by a lack of appropriate funding,[21] a lack of understanding as to the proper undertaking of VR services,[10,12] and a lack of awareness on the injured person's part, or the care provider's, of the applicability of VR services.[19] Reported rates of RTW vary considerably in the literature, depending upon the population studied and limitations of individual study methodologies.[22] RTW is reported to range from 20% to 100%.

Vocation serves a tremendously important role in life, yet VR is one of the least understood and least delivered services for people with TBI. This chapter addresses the provision of VR services to individuals with TBI.

EMPLOYMENT TRENDS FOLLOWING TBI

RTW following TBI is not easily accomplished and may not be accomplished by some individuals. Rates of RTW vary throughout the literature and are impacted by both the definition of "work" and the nature of the population studied. Rates of RTW have emotional, financial, and social implications. In a study by Johnstone, Mount, and Schopp, TBI was associated with an estimated $642 million in lost wages, $96 million in lost income taxes, and $353 million in increased public assistance secondary to unemployment 1 year postinjury.[23] Corrigan et al. report that a review of 2004 annual findings from the Traumatic Brain Injury Model Systems (TBIMS) national data set for the United States showed competitive employment at 1 year after injury for 27% of individuals and 29% at 5 years postinjury.[24] Review of the TBIMS data set for collected case data through 2007 showed competitive employment at 1 year for 28% and 33% at 2 years postinjury (TBIMS 2008 report).[25]

A 2009 systematic review by van Velzen et al.[26] of more than 2,000 studies found employment rates for people with TBI to be 40.7% at 1 year postinjury and 40.8% at 2 years postinjury overall with many people having difficulty returning to their preinjury place of employment. People with brain injury who did not return to work had either been unable to sustain employment or were unable to return to work at all. Grauwmeijer et al. conducted a 3-year prospective employment of 113 people with moderate-to-severe TBI.[27] Of the cohort who completed the study, 55% were employed at 3 years postinjury. They found that the biggest risk factors for return to employment were impaired cognitive status and psychiatric symptoms and the time of discharge from the hospital. Shigaki et al. conducted a

longitudinal employment study of 49 people with TBI and found a 38% employment rate at 2 years postinjury with lower wages compared to baseline.[28] Interestingly, they found that when compared with 1-year postinjury, wages had increased significantly at 2 years across the cohort, likely secondary to public funding, further emphasizing the financial burden that TBI places on the public in addition to the individuals with brain injury.

The timing of VR involvement may impact RTW.[29] Individuals for whom VR services were provided within a year of injury had a better rate of RTW than those who received services after 1 year.[30] Reid-Arndt et al. reviewed differences between early referral VR candidates with TBI to late referral candidates.[31] Early referral candidates averaged 10.6 months from injury with 40% being within 90 days of injury and were enrolled an average of 19.4 months in the program. Late referral candidates averaged 58.1 months and were enrolled at an average of 29.9 months. The early referral group reported significantly more hours of competitive pay per week and more weeks of competitive employment. Both groups, however, reported very low numbers: 5.11 paid hours per week and 7.85 weeks per year for the early referral group and 4.18 paid hours per week and 2.19 weeks per year for the late referral group. In 2015, van Velzen et al. proposed a protocol for early vocational intervention for people with acquired brain injury (ABI) that could be trialed and implemented in inpatient and outpatient rehabilitation centers.[32] The Early Vocational Rehabilitation (EVR) protocol consists of four stages: 1) orientation of the rehabilitation team toward the nature of the patient's work, 2) investigating the gaps between the patient's abilities and work, 3) work training, and 4) finalizing the EVR once the patient is under the guidance of his or her employer and/or physician with recommendations as needed for ongoing treatments. The protocol was trialed in an interdisciplinary rehabilitation program with 23 patients who were employed prior to their injury. Questionnaires were given to patients and providers following the protocol, and 94% reported suitability of this protocol for regular use with the structured approach in the early phases of rehabilitation as its biggest strength.

RTW by an individual following TBI can also be complicated by difficulty in maintaining employment. Studies listed previously note a number of individuals who had returned to work but did not disclose the nature of difficulties encountered while at work or in maintaining the vocational placement. Forslund et al. report stably employed rates of 39%, unstably employed rates of 44%, and unemployed rates of 17% in a group of individuals treated in Norway.[33] Sale et al. followed 29 people with moderate-to-severe TBI and studied reasons for job separations.[34] Average age at injury was 25.65 years, and average age at the time of the study was 33.07 years at an average of 7.42 years postinjury. Coma duration for the group averaged 48.2 days. Educational level achieved was as follows: some high school, seven people; high school graduate, eight people; some college, ten people; college graduate, three people; and unknown, one person. Only medically stable individuals and those who were not actively abusing substances were included in the study. This group experienced 38 individual job separations. The mean length of employment noted before job separation was 5.8 months with a range observed of 0.2 months to 27.6 months. Fully two thirds of all job separations came within the first 6 months of employment. The most frequently cited reason for job separation was interpersonal relationship difficulties. These included displays of anger, inappropriate social interaction, and overfamiliarity. Additional reasons for job separation included economic layoffs, substance abuse, criminal activity, and mental health problems. Employment tends to decline over time as a consequence of these problems.

Ben-Yishay et al. reviewed a group of 94 individuals with diffuse brain injuries.[20] Average age was 27 years (range 15–60 years), education level averaged 14 years (range 8–20 years), coma duration averaged 34.40 days (range 1–120 days), and time from injury to admission averaged 36.46 months (range 4–207 months). Eligibility for program admission required a verbal or performance IQ of at least 80, ambulatory capability, no required physical restraints, and ability to reliably engage in two-way verbal communication. Patients were excluded with a history of a previous brain injury, significant psychiatric history, or significant history of drug/alcohol abuse. The authors found a drop from 64% competitive employment immediately following program completion to 50% at 3 years postdischarge. A similar decline was noted in noncompetitive employment placements from 30% at discharge to 22% by year 3. Principal causes of a lack of work stability were 1) social isolation manifest by alcohol abuse, disinhibition phenomena, and temporary psychiatric complications; 2) forgetting to use acquired strategies manifest as ill-advised attempts to resume high-level academic studies and counterproductive and obsessive quests for remediating intractable deficits; and 3) financial disincentives to work manifest by extravagant spending binges of settlement funds and anticipation of large settlement proceeds from pending litigation.

West reviewed 37 individuals who were placed in supported employment.[35] Only 19 (51%) of these individuals retained their jobs at 6 months. In a comparison of those individuals who remained employed to those who lost employment, there was no significant difference found between the groups with reference to race, marital status, highest educational level achieved, residential situation, community type, cause of injury, injury severity, work status prior to injury, or work status prior to referral to the supported employment project. Although there was a difference in average age, with the younger group tending toward employment retention, the difference was not statistically significant. Almost all the participants were employed in entry-level unskilled or semiskilled positions. The study reviewed the integration of the individual into the jobsite, workforce position, and monetary benefits associated with employment. Inequities of the workplace and opportunities for monetary and nonmonetary benefits were found to be factors in job retention of supported individuals. Job retention outcomes appeared to be better for those individuals

placed in positions offering fringe benefits, opportunities for raises and advancement, formal and informal support, and opportunities for socialization.

Wall et al. reviewed 31 individuals with TBI and seven with ABI arising from cardiovascular accident (CVA) or chronic neurological conditions who participated in a community-based training program.[36] Injury severity was not provided. Mean time since injury was 10 years and since diagnosis was 8.91 years. Median number of years of education was 12.0, and mean preinjury work history was 31.44 months. Fifty-eight percent received income from a federally funded program, averaging $439 monthly. Thirty-seven percent were working at injury or onset of illness. The average program duration was 10.54 weeks with 58% completing the program. Those who completed the program differed only in that they had a longer duration of disability and longer preinjury work histories. A total of 67% of persons who completed the program retained their job at 60 days and 59% at about 18 months out. Mean starting salary was $5.68 per hour. Approximately half of those who did not complete the program reported substance abuse.

As can be seen, difficulties with employment following TBI are a common finding in both short- and long-term studies. The nature of the neurological injuries sustained, inadequacies of VR programming, and shortcomings of medical rehabilitation programming resulting in failure to provide adequate assistance in recovery from TBI contribute to re-employment difficulties. It is safe to assume that the neurological injuries sustained impact the degree to which recovery can be expected. Comparatively less research has focused on the latter two factors. It appears, however, that competitive employment after TBI is difficult for most and impossible for many. Programmed interventions appear to be successful at improving the overall RTW rate and, to a lesser degree, job retention. Great care must be taken in review of the RTW literature in TBI due to tremendous variability in the manner in which this topic is reported.[37]

PROGNOSTICATING RTW

Recovery from TBI can occur over protracted periods of time.[38–40] Consequently, no reliable means of determining exactly when VR services should be undertaken exists. Unfortunately, however, injured individuals, families, and professionals share a common concern for identifying the long-term, perhaps ultimate, recovery potential following injury. These questions begin very soon after injury and persist for many months, if not years. RTW is impacted both by the nature of the sequelae from the TBI as well as noninjury-related factors.

An awareness of prognostic variables impacting individuals with TBI can help determine the intensity and type of VR services to be delivered.[41] Gonser reviewed both cognitive and physical disabilities as prognostic factors in vocational return and suggested that neuropsychological impairment was the single most important factor in the prognostication of the vocational return.[42] Machamer et al. followed 165 workers with mild-to-severe TBI and found that higher neuropsychological functioning 1 month post-injury combined with higher premorbid functioning and lower severity of injury resulted in higher stability of employment.[43] Ruff et al. also found neuropsychological function to be important in RTW.[44] They reviewed predictors of outcome following severe head injury and found age, WAIS-R vocabulary score, and selective attention speed combined to correctly classify 88% of subjects in a category of either productive or nonproductive work.

Age at injury has been often offered as a prognostic variable in RTW.[41,44–48] Most studies support the idea that a direct correlation exists between age and RTW.[41,44–48] Individuals who are younger at the time of injury are more likely to progress to RTW than individuals who are older.[41] Preinjury employment status and educational level have been demonstrated to be strong predictors of RTW.[41] Individuals who were employed at the time of injury and individuals with higher educational achievement were more likely to return to work than individuals who were unemployed at the time of injury, had poor employment history, or had lesser educational achievement. Keyser-Marcus et al. found individuals who were employed at the time of injury were three to five times more likely to be employed postinjury.[41] A partial explanation for this finding may be that, following brain injury, information that was well learned at the time of injury is more readily called upon by the individual in contrast to information that must be acquired following injury and reliance upon new learning skills. This can be of great assistance in returning an individual to work, in particular, in instances in which the work to be performed by the individual relies upon old information and has little demand for new learning. As such, rote tasks will be largely more successful in RTW scenarios than those tasks that require a high dependence on new learning. Conversely, some positions require much greater reliance on new information processing and will not benefit from dependence upon rote tasks.[49]

Coma duration has been documented as a prognostic variable for overall outcome following TBI and for RTW. Shorter coma durations are associated with greater likelihood of RTW. Similarly, duration of posttraumatic amnesia (PTA) has been correlated to RTW[50] as has duration of acute rehabilitation treatment.[41,51] Again, in both instances, shorter periods are associated with a greater likelihood of RTW. Rao et al. noted that fewer positive findings on CT scan correlated with RTW.[52]

Length of stay (LOS) has been studied as a potential predictor variable to vocational outcome. A systematic review by van Velzen et al. found LOS as a strong predictor of vocational outcome.[53] Keyser-Marcus et al. reported that rehabilitation LOS predicted RTW at 1 year postinjury; shorter LOS was associated with RTW.[41] Although it might be argued that LOS is an indirect measure of injury severity, more direct measures of injury severity, such as Glasgow Coma Score (GCS) and duration of PTA, were not predictive of RTW. These findings support those of Gollaher et al.[22] and Ip et al.[54] GCS has not been found to be highly predictive of

outcome, in particular for those individuals who are in the moderate range of severity of injury.[55] The utility of PTA for long-term functional prediction has also been questioned.[56] Gollaher et al. utilized a functional outcome measure, the Disability Rating Scale (DRS), which is based upon the GCS but further discriminates higher functional levels.[22–57] Educational level, admission DRS, discharge DRS, and preinjury productivity allowed correct classification of 84% for employed subjects, 66% for unemployed subjects, and 75% across both groups. Leung and Man also determined that the DRS, in combination with the Neurobehavioral Cognitive Status Examination (Cognistat), and premorbid occupation were significant predictors of RTW that allowed correct classification of 65.8% of subjects in a 79-subject study.[58] A study by Hofgren et al. looked not only at LOS, but also at activities of daily living (ADL) independence at discharge from rehabilitation.[59] They found that patients who achieved ADL independence were able to return to employment, emphasizing the need to invest in early rehabilitation efforts.[53,59]

The relationship between severity of injury and the vocational outcome is not linear.[60] Generally speaking, when impairment level at 24 hours postinjury is related to productivity at follow-up, a relationship is found that more severe impairment leads to less productivity. Some notable exceptions exist, however, in that some individuals who are severely impaired at 24 hours postinjury achieve good outcomes, and comparatively less severely impaired individuals suffer poorer outcomes. In a study by Sherer et al., initial severity of injury did not significantly predict postinjury productivity.[61] Individuals in their sample ranged from mild-to-severe TBI, and all were involved in postacute rehabilitation programs. Education level, preinjury substance abuse, need for behavioral supervision, and need for physical supervision all correlated with productivity status. Interestingly, when adjusting for the effects of all other predictors, preinjury substance abuse emerged as the only significant predictor of productivity. Substance abuse has emerged as a predictor in several other studies as well.[34,61–63] Sherer et al. cited possible selection bias in the study compared to other studies in which severity of injury was found to be indicative of RTW.[61] The fact remains, however, that many moderately to severely injured individuals were found to be unable to successfully return to work when evaluated some 2 years postinjury.[64] Felmingham et al. agreed that severity of injury impacted outcome but only when paired with age.[45]

Dawson et al. investigated determinants and correlates of return to productivity postinjury in 46 individuals with TBI.[65] Injury severity was found to be a significant predictor for return to productivity as well as physical, psychological, and spiritual factors. It is important to note that psychological well-being is often a subjective experience and is a noted predictor of RTW status. Because of this, collecting subjective information related to mood, fatigue, and behavior may be more valuable, at times, in predicting RTW than objective measures.[66] These factors can often become amplified following acute rehabilitation and can enhance prognostic predictability. Felmingham et al. found that adding postdischarge predictors to acute variables improved the ability to predict work status 2 years after rehabilitation, particularly regarding psychological well-being. Those noted to have better adjustment tended to perform better in the work force. In a similar vein, some have noted that individuals who had difficulty with awareness and acceptance of deficits associated with TBI were less likely to experience vocational success.[67,68] Felmingham et al.[69] concluded that severity of injury (only when paired with age), age at the time of injury, premorbid employment status or work status at 6 months postinjury, and level of psychological distress 6 months postdischarge from a rehabilitation hospital setting were significant predictors of RTW. Devitt et al. also suggest comprehensively assessing pre- and postinjury predictors to predict occupational performance.[70] Ownsworth and McKenna reviewed the literature to determine factors most consistently related to employment outcomes in TBI pre- and postinjury.[71] They concluded that preinjury occupational status, functional status at discharge, global cognitive functioning, perceptual ability, executive functioning, involvement in vocational services, and emotional status were most likely to impact RTW.

Forslund et al. performed a longitudinal cohort study of 105 individuals with moderate-to-severe TBI and their employment status at 1, 2, and 5 years postinjury. They found lower GCS at admission and longer duration of PTA were significantly associated with unemployment. In addition, social factors, such as being single, being unemployed at the time of injury, and also working a blue-collar job, were also associated with unemployment. The factors of injury severity (GCS, PTA, LOS) were also found to be negatively associated with job stability over time in the cohort studied. Conversely, individuals who were married or partnered, employed, or in white collar positions at the time of injury were more likely to be employed at each of the time points.

In summary, the research literature implicates age, severity of injury, coma duration, duration of acute rehabilitation, duration of PTA, postacute adjustment, awareness and acceptance of deficits, substance abuse, premorbid work status, educational attainment, marital status and functional status in the prognostication of RTW. It is clear that no single variable has predictive power sufficient to be used independently of the others. Many of the above variables essentially implicate the overall severity of injury although not all. There are, nonetheless, notable exceptions in instances in which persons with less severe injuries face difficulty in RTW and when psychosocial circumstances or issues, such as substance abuse and family and community supports or financial need to return to work, intervene. Regardless of the factors involved, comprehensive rehabilitation with vocational services can improve outcomes.[68]

INDUSTRY-RELATED FACTORS INFLUENCING RTW

Individuals with TBI may not be familiar with VR services and vice versa. In a survey of 620 traumatically brain-injured

individuals who were 1 year postinjury, only 34% were aware of the existence of VR services.[19] Those involved in outpatient or postacute rehabilitation and those who were employed preinjury were more likely to be aware of available services. Ironically, VR counselors (VRCs) appear to be similarly unaware of the needs of people with TBI. Hallauer et al. found that most VRCs lack experience with TBI.[10] Most counselors surveyed had work experience with fewer than 10 TBI clients. Counselors tended to overattribute problems in memory dysfunction even in the absence of supportive test findings.

In a survey that involved the New York State Office of Vocational Rehabilitation,[12] the VR program success for 47 individuals with TBI was reviewed. Only 8.5% of the individuals who received services were ultimately placed in jobs. The VRCs, as a group, reported factual unawareness of the need for cognitive remedial services for this population. These professionals were keenly aware that they did not have specific programs developed to address the needs of the individual with TBI.

The need to bring VRCs and medical rehabilitation teams together has been suggested by a number of authors.[72–74] Each of these groups provides coordinated interdisciplinary care. The knowledge base of the VRC can be materially increased in this manner.[74] An additional mismatch can be found between the perceptions of VRCs and employers.[75] Employers' primary concerns had to do with whether the individual could actually fulfill the job responsibilities. Concerns of VRCs, however, tended to focus on workplace accommodations. Last, one study indicated failed VR programs tended to be too short in duration or too long postinjury to be effective.[76]

Lack of availability of rehabilitation services, division of responsibility for rehabilitation between several governmental and private sector agencies, economical decline, employer's fitness requirements, disability discrimination, delayed or ineffectual management of treatable diseases and conditions, and disability compensation benefits can all contribute to failure to return to work.[77–83] Numerous articles have suggested the potential contribution of compensation in failure to return to work in the general population.[13,80–84] Although care must be taken in interpretation of these ideas, there are clearly some discrepancies in RTW that are difficult to explain, namely those found in RTW of people with mild-to-moderate TBI. There are differences in RTW rates for those people receiving disability and social security benefits and those who do not,[80,82] and some find VR to be a potentially destabilizing threat to their financial status and eligibility for public health care coverage, such as Medicaid or Medicare.[81]

In summary, at the point of involvement of VR, the individual with TBI may or may not have participated in medical rehabilitation. Participation in medical rehabilitation cannot be guaranteed, especially for those individuals who might be referred to departments of VR without adequate documentation of the previous TBI. Once involved in the VR process, placement may not be achieved or maintained due to 1) inadequate resolution of sequelae of the TBI; 2) awareness by individuals with TBI, their families, medical rehabilitation professionals, or VR professionals of the need for VR services; 3) knowledge on the part of the VRC as to how to pursue job placement for individuals with TBI; 4) failure of the job placement to meet the esteem and financial needs of the injured worker; 5) socially inappropriate or unacceptable behaviors; 6) a mismatch between the focus of the VRC and the needs of the employer; 7) financial disincentives to return to work; or 8) a societal predisposition toward continued unemployment due to divergent agency goals or insufficient public expenditures to support RTW efforts. This list is by no means exhaustive or complete and, as such, points to the tremendous complexity of returning an individual with TBI to work.

VR PREREQUISITES

Readiness for VR, of course, involves identification and treatment of deficits following TBI—and more. In many jurisdictions, state legislatures have enacted rules that must be followed, in particular, when individuals are injured in the course of their employment. The VRC and, in some instances, medical rehabilitation providers should be familiar with reporting requirements and be able to comply with the various filings that may be required.

Ideally, the VR process begins during the medical rehabilitation of individuals with TBI. The VRC should be familiar with the goals and plans of the medical rehabilitation team from an early point in the rehabilitation process. Likewise, the medical rehabilitation team can obtain insight from the VRC regarding the injured individual's personality, social status, educational attainment, socialization skills, and vocational aptitudes, all of which may bear upon medical rehabilitation goal setting. Rehabilitation teams often focus on "functional" capabilities, and achievement of a "functional" level of independence may not be sufficient to allow successful RTW.

An early review of an individual's deficits may allow a VRC timely recognition of those barriers to RTW that are likely to be overcome and those that are less likely. In instances in which the individual is unlikely to return to a previous vocational setting, introduction of this idea to the injured individual and the family may allow for professional assistance with adjustment and better financial planning for the family. Adjustment to disability can be quite difficult, and some people with TBI are reluctant to accept that their level of functioning may not be sufficient to allow a return to a previous level of employment.[45,67,85] Often, clients are unwilling to shift their expectations for RTW and can be resistant to rehabilitation plans that move in a direction other than return to previous employment. Medical rehabilitation providers can be quite helpful in assisting with adjustment issues and creatively addressing barriers to employment or development of vocational alternatives. The interplay between the vocational and medical rehabilitation professionals with the individual and his or her family can

best ensure that the highest levels of independence and life satisfaction are incorporated into goal setting.

The VRC should work with medical rehabilitation professionals to conduct prevocational testing. Prevocational testing can be invaluable in identifying barriers to RTW for all parties. A host of standardized and subjective assessments can be utilized in this pursuit, and detailed information can be obtained that spells out deficits that will impact RTW. The allied health disciplines of occupational therapy, physical therapy, speech therapy, therapeutic recreation, educational therapy, clinical psychology, and neuropsychology can also provide insight into likely problem areas. Situational assessment to confirm test findings should be considered during prevocational testing.[86] Additionally, a review of a thorough job description, together with functional observation and the comprehensive interview, should accompany neuropsychological evaluation as the VRC attempts to discern vocational readiness and aptitude.[46] Care must be taken in evaluating people with TBI to avoid an overreliance on standardized testing. One study suggested that 38% of VRCs surveyed relied, either moderately or very heavily, on standardized testing.[12] A learning-style evaluation during prevocational testing may be helpful in determining optimal and nonoptimal strategy development for presentation of new learning.[46,87] To that end, the degree to which an intended vocational placement relies upon rote activities versus new learning should be considered. Based on prevocational testing results, obtainment of further rehabilitative treatment may be necessary to better prepare people for success in the workplace.

Using the ICF model to inform RTW planning and interventions

The International Classification of Functioning, Disability, and Health (ICF) provides a helpful framework and terminology for RTW planning and interventions.[88–90] This framework can also provide a useful basis for making RTW research in TBI more homogeneous.[88] By understanding how brain injury impacts body functions, activities, and participation in relation to RTW and by understanding the related influence of personal and environmental factors involved, better, individualized decisions can be made for programming, intervention, and possible prognostication.

Andelic et al. looked at 93 people with TBI and their RTW status at 1-year postinjury using the ICF model.[89] They performed evaluations that looked at body functions (impairments, such as brain injury severity, trauma severity, and number of overall impairments), activities (limitations in cognitive and motor abilities), and participation (community integration). They also compared these with personal factors (age, gender, preinjury employment status). They found that 53% of their subjects were employed at 1-year postinjury. They found that the group that was employed had fewer impairments in body function and were more independent in their cognitive and motor functions. Participation restrictions were not as significant. Using all of these ICF factors, they found that they could predict with 86% accuracy a person's likelihood of returning to work.

Forslund et al. completed a prospective study of 100 people with moderate-to-severe TBI, examining the impact of personal and environmental factors on RTW at 1 and 2 years postinjury.[90] They found that at 2 years, 44% of people had returned to work. They found that the personal factors of preinjury employment and severity of injury were the most significant in RTW. Of the environmental factors, they found that the strong presence of friends, a lesser need of coordinated health services (lower severity of injury), and the ability to drive a car were the most significant. Further research in the realm of environmental factors was recommended to improve programming. Lundquist and Samuelsson also examined personal and societal factors influencing RTW from the perspective of patients and professionals.[91] They found that the personal and social factors were synergistic in nature and emphasized the societal and contextual factors as key for successful VR.

The literature using the ICF model/terminology for RTW emphasizes mindful evaluation of each aspect. Not every aspect, however, especially personal factors, can be changed or influenced through a rehabilitation program. Treatment should focus on being aware of all factors and then trying to change or improve ones that are susceptible to influence. For example, some body functions and activity limitations can improve through skilled intervention, therefore improving participation. Some environmental factors can be changed such as accessibility, assistive technology, or job modifications to improve RTW outcome and overall participation. A blend of medical rehabilitation and social rehabilitation can be justified using this model.

INJURY-RELATED FACTORS INFLUENCING RTW

Introduction of VR services typically occurs at a time determined by medical rehabilitation professionals. Although, on the surface, this may seem logical, the approach is problematic in those instances in which, well meaning although poorly informed, professionals believe that the medical rehabilitation has, in fact, resulted in a readiness for VR. Unfortunately, all too often, this is not the case, and individuals with TBI are prematurely returned to work and subjected unnecessarily to failure. This is clearly demonstrated in the literature reviewed thus far.

The typical approach taken in VR is to attempt to achieve medical stability prior to undertaking VR services. Recovery from TBI, however, seldom finds an individual at a point at which a clear demarcation exists between the end of medical treatment and readiness for VR. The complexity of deficits seen following TBI complicates the delineation of the starting point for VR.

The constellation of deficits seen following TBI can include motor, cognitive, communicative, psychosocial, psychological, and behavioral impairments.[7,92] Some of these deficits will persist in some fashion despite the best

efforts at medical rehabilitation. Cognitive deficits, physical deficits, and personality changes contribute to failure in RTW.[7,18,93–97] Of course, severity of injury may impact both the number of deficits and their persistence, although there is not necessarily a direct relationship between severity of injury and likelihood of RTW.[41,45,62]

Physical deficits

Given the shortened time frames in rehabilitation of people with TBI,[98-100] therapists are forced to focus on functional capabilities for performance of basic self-care and daily routines as a primary goal. Rarely will goals beyond these be a consideration early in the rehabilitation of a person with TBI, largely due to funding and utilization review constraints. Although the world has become much more "accessible" for people with physical disabilities, optimization of physical functioning following TBI via extended therapy can be quite important in returning to work. Wehman et al. discerned that an individual's level of functional limitations impacted the likelihood of RTW.[48] Just as physical and cognitive limitations would impair functional capabilities with reference to self-care skills, these limitations appeared to ultimately culminate in difficulties in RTW as well. Physical limitations can bring about significant challenge to self-concept, body image, and social interactions, all of which are likely to impact RTW.[101] The VRC is in a unique position to advocate for such additional interventions.

McNamee et al. evaluated the most common physical sequelae that affect RTW after TBI and grouped them for mild and moderate-to-severe TBI.[102] For mild TBI, he found headaches, vision deficits, pain syndromes, dizziness, and postural instability. For moderate-to-severe TBI, he found heterotopic ossification, hypertonicity, seizures, postural instability, fine motor deficits, visual deficits, insomnia, and fatigue. The VRC must consider all of these factors and be aware of their impact on work reintegration. The individual must be able to move about the workplace freely and safely. The highest level of ambulation with the least reliance upon aids should be sought. Canes, walkers, and wheelchairs, although designed to enhance environmental access, unfortunately may contribute to workplace biases about an individual's inherent abilities. More pragmatically, such devices can raise questions in an employer's mind regarding safety.

Balance, coordination, and vestibular function must be such that the person is not experiencing dizziness that could impede the ability to move about the workplace or complete various job tasks.[103] Chamelian and Feinstein found that dizziness can cause significant emotional distress postinjury and may be an independent predictor of failure to return to work.[104] Dehail et al. reviewed 68 consecutive admissions of individuals with TBI to a VR program compared to 52 healthy, age-matched controls.[105] Mean age of the TBI group was 33.2 years with a mean chronicity since injury of 55.2 months. GCS for the group averaged 6.6; however, GCS was less than 8 for 60 of the 68. One third of the individuals with severe TBI complained of vertigo, dizziness, or balance instability at admission. Clinical examination found impairments in 17 of these and none in nine. Of those who had no complaints of vertigo, dizziness, or balance instability, clinical examination showed impairments in 19 cases. There were no demonstrable correlations between any posturographic parameter and age, gender, scores on cognitive tests, brain MRI or CT abnormality, or psychotropic treatment. There were no correlations for those with or without complaints. It was clear that visual deprivation contributed strongly to posturographic findings. Individual awareness of deficits could not be relied upon for either confirmation of deficits of balance or for a lack thereof. The findings of Dehail et al. bear significantly on risks associated with RTW, in particular for reinjury. Individuals who may need to work in low-light conditions may be particularly vulnerable. Individuals cannot be relied upon to accurately report deficits that may place them and their employer at risk. Confirmation of a lack of balance problems should be obtained by the VRC. Of course, such impairments may preclude return to certain jobs, such as those that require climbing ladders or working at heights. Physical therapy and medical treatment can be quite beneficial in improving functional capacity for balance disorders following TBI and can improve protective reactions. Care should be taken to avoid reliance solely upon medications that reduce the experience of dizziness as these medications act only to reduce the symptoms rather than improve the underlying condition. Consequently, impaired protective reactions continue to be present, thereby increasing the likelihood of reinjury.

Perceptual deficits in either vision or hearing can also impact successful job task completion, socialization, communication, and safety. In some workplaces, the sense of smell is important to safety (e.g., in working with combustible liquids or gases) and may be integral to actual job task completion (e.g., in food preparation or storage responsibilities).

Muscular and cardiorespiratory endurance will materially impact job performance and mental acuity. Fatigue is a frequently reported component of TBI impairment.[7] Deconditioning following prolonged disability is common and should be assessed and addressed prior to RTW. Most jobs require a fairly high level of manual dexterity. As such, dexterity must be considered as well as adaptations that may be appropriate to a specific job description. Further detailed information about treatment of physical deficits can be found in Chapter 29.

Finally, it is important to address the impact of fatigue on RTW. Up to 73% of people with TBI experience fatigue 5 years after injury. The long-standing effects of fatigue impact both physical and psychological functioning. In a study of 223 people with mild-to-severe TBI, Cantor et al. found that postinjury fatigue negatively impacted subjective reports of quality of life.[106] They also found, however, that fatigue did not negatively impact participation in desired life activities, meaning that fatigue was not stopping people from participating in life but negatively impacted the quality of

participation. Ziino and Ponsford found that fatigue reduced the quality of performance on selective attention tasks and other complex cognitive tasks independent of mood. These types of tasks are common in the workplace.[107] With appropriate rehabilitation and structured routines, fatigue in the workplace can be managed to allow for improved quality of participation. Strategies for fatigue management include controlling cognitive processing demands by practicing tasks until they are well learned, reducing cognitive processing demands by simplifying tasks,[107] and building in frequent rest breaks.

Psychological and behavioral issues

TBI can cause significant disruption of function in the psychological and psychiatric realm, resulting in deficits in interpersonal, social, and occupational function.[108] Psychiatric disorders as a comorbidity with TBI has a strong negative association with successful RTW.[109] Thorough rehabilitation for people with TBI may include psychiatric, psychological, and neuropsychological evaluation and interventions. Personality and neuropsychological testing that utilizes input from the client, family, friends, and coworkers will provide the greatest level of understanding for all rehabilitation professionals involved. Care should be taken, however, to avoid over-reliance on neuropsychological test results for the determination of vocational aptitude or readiness.[86,110] Neuropsychological findings are best used in conjunction with observation of function in real-world settings. It is not uncommon following TBI to need to provide psychological interventions for awareness of and adjustment to disability,[111–113] motivation, sexuality, stress management, fear, interpersonal relationship management, depression,[114,115] substance abuse,[114] lifestyle changes, irritability and loss of temper,[7] family issues, parenting,[116] coping style,[117] spousal relationships,[118] anxiety,[114] and goal setting. The VRC may play a role in many of these areas, either in providing some of the counseling or provision of insight into some of these areas to other psychology staff.

Evaluative tools, such as the Minnesota Multiphasic Personality Inventory II (MMPI-II),[119] the Taylor-Johnson Temperament Analysis,[120] the Fundamental Interpersonal Relations Orientation-Behavior Scale,[121] and the Beck Depression Scale,[122] can be useful in understanding variables that may be barriers to RTW. Care should be taken in interpretation of the MMPI-II as deficits following TBI can, fairly predictably, elevate specific scales, such as depression, hypochondriasis/somatization, schizophrenia, and psychosis.[123] Some have suggested that scoring of the MMPI for this population should be altered for this reason.[124–126] The tool can be useful, nonetheless, in a careful consideration of its findings coupled with information from the clinical observations of allied health professionals and family.

TBI is overwhelming in its impact upon the individual, and coping with the seemingly total change in one's abilities and lifestyle is arduous and grueling. Adaptation to such profound changes in one's life can take a lifetime, yet rehabilitation demands such accommodation in months. The VRC should have sufficient background to be able to identify when phases of the VR process will be too challenging or likely to elicit maladaptive responses or adjustment opportunities. For example, a person placed in an employment position by a VRC who knows the placement will fail may yield either an improved awareness of remaining areas of deficit to be worked on in therapy or a humiliation that strips the individual of all motivation. The difference between these two outcomes should be predicted by the VRC, who is aware of the psychological status of the injured worker. Prevocational counseling allows for such insight to be gained by the counselor. The counselor may be in a position to recommend the involvement of a counselor or psychologist for rigorous investigation and treatment of issues pertaining to attitudes toward RTW, motivation, adjustment to disability, and so on. Given the pervasive and all-encompassing nature the impact that TBI has on one's life, all but the rarest of individuals will benefit from some assistance in handling the psychological burden.

Participation in therapy following TBI is difficult, and some people suffer from motivational challenges to continue therapeutic endeavors. The appropriately designed VR plan can be helpful to some in coming to an understanding of why seemingly useless therapy tasks will benefit them when they return to work. Conversely, although the proper timing of RTW has been emphasized, there are some instances in which motivation to complete therapy tasks and goals can be enhanced by engaging the person in some part-time, perhaps lower level, RTW that is meaningfully associated with or drawn from their intended final vocational placement. Participation in the workplace exercises, in effect, all the skills that are the focus of therapeutic endeavors. Such placements, conducted coincidentally with therapy, can allow the individual to gradually realize limitations and the relationship between those limitations, successful completion of therapy tasks to address those limitations, and success in the workplace.

The individual's financial needs and status must be well understood prior to undertaking VR.[79–83] This includes a review of all sources of income, including income that may derive from pending legal proceedings. The individual's financial well-being should be considered together with the benefits that come from independence and self-reliance. An ethical quagmire can readily emerge in these considerations, and the VRC should be well-versed in both legal requirements that may impact vocational planning and ethical issues that ought to guide the counselor's approach to a case. An excellent review of ethical issues can be found in Chapter 36.

Motivational concerns that may present as challenges to a successful vocational plan can arise from both questionable and legitimate issues. In a study of 37 individuals with TBI in supported employment settings, West concluded that a primary factor distinguishing those who retained employment after 6 months from those who did not could be found in whether the positions individuals were placed in offered

fringe benefits, opportunities for raises and advancement, formal and informal support, and opportunities for socialization with other employees.[35] There were no statistically significant differences between the two groups in race, marital status, highest educational level achieved, residential status, community type, cause or severity of injury, work status prior to injury or prior to referral to supported employment, or age. The small size of the subject pool, however, is an important consideration. West pointed out that career development differs from job placement. The degree to which both are driven by the individual's goals and motivation will heighten the likelihood that positions that will hold the individual's interest will inspire good work skills and behaviors, thereby promoting long-term success. As indicated earlier, the primary reasons for job separation from the first and second employment opportunities are related to interpersonal skills. Maintenance of personal boundaries can be difficult for the person with TBI. This includes respecting personal space, identifying body language that signals continued or waning interest in a conversational topic, respecting overt requests for changes in topic or cessation of a discussion, engaging in appropriate social pleasantries, respecting professional relationships and avoiding overly familiar behaviors, proper usage of manners, control of emotional lability, and impulse control.

Social skills are acquired over a lifetime and are continuously updated. Social judgment is crucial in the workplace as it represents a primary source of socialization for most people. Social skills used on the job are considerably different than those used in the home environment, and there is a clear demarcation of expectations between these two environments. TBI often impairs a person's ability to pick up on social cues, such as body language, facial expression, and subtle linguistic cues that may be given.[59] Failure to identify these cues will readily result in social isolation and failure, which obviously will impact both the injured person's ability to complete job tasks successfully and his or her derivation of personal satisfaction and self-esteem from the workplace.

Differences in level of socialization have been identified with different types of supported employment environment.[127] Individual, enclave, and work crew-supported employment environments were analyzed for the amount of contact between disabled and nondisabled workers. Individual and enclave environments showed substantially more interaction between coworkers than work crew environments. Individual and enclave environments might be more conducive to social integration, a key component in job retention and life satisfaction. Because job separations are common following TBI and RTW occurs for only a portion of those injured, care must be taken not to jeopardize availability of financial support from such sources as Social Security, disability insurance policies, or permanent disability payments from workers' compensation claims. Dikmen et al.[64] reported on the earnings of 31 individuals with moderate-to-severe brain injury following 2 years postinjury. Although the group was no different than a control group in earnings prior to injury, earnings were substantially below those of the control group at 1 year. Earnings improved slightly by year 2 although they remained substantially below the control group. Ashley et al. conducted a follow-up study of 332 people with TBI who averaged 7.1 years postinjury and 5.3 years postdischarge.[128] The group was heavily biased in that all participants had access to treatment funding from workers' compensation, accident and health, or liability insurance coverage. The study showed that only 83.9% of respondents reported they were financially "getting by or better." The estimated mean of monthly income loss per family was $1,058 in 1997 dollars, and the mean household earnings was decreased by about $402, suggesting that others in the family had become employed or changed employment to higher-paying positions.

TBI regularly places families below the median income level and often into poverty levels. In the study by Ashley et al.,[128] 16.1% of respondents reported increased indebtedness, and 7.4% required public assistance for medical costs.[128] These numbers can be reasonably assumed to be much higher for the TBI population in general.

Income stability can become an issue in the case of people who were employed in seasonal positions. Those people who are covered by workers' compensation may acquire a more stable income source following injury. In some cases, prolonged medical disability translates to prolonged maintenance of immigration status. In still others, psychological benefits accrue from being dependent upon a spouse or parent, or conversely, spouses or other family members may derive some psychological or financial benefit from continued levels of dependency, such as when family members are paid for care of an injured person.

Cognitive deficits

Cognitive rehabilitation following TBI represents one of the greatest challenges facing allied health professionals and people with TBI. Cognitive function impacts all aspects of daily living, social interaction, psychological function and adjustment, communication, and, of course, work. Rehabilitative efforts in cognition can be both compensatory and remediative.[129–131] Rehabilitation of cognitive function requires medical stability and a great deal of therapeutic effort. The most successful cognitive rehabilitation takes place over months rather than weeks. Compensatory strategies may be developed, in some instances, to support the injured worker in job performance; however, some levels of cognitive dysfunction are less amenable to compensatory approaches. A realistic appraisal of the likelihood of success is crucial.

Cognitive deficits, such as problems with attention, concentration, persistence, problem solving, judgment, reasoning, memory, and self-regulation of behavior, will all detrimentally affect the injured worker's ability to perform on the job.[37,132] Such deficits can be present in people without any obvious physical impairments and can be camouflaged by intact expressive language skills. Bjerke found a lack of correspondence between neuropsychological test

results and levels of reported memory function for people with TBI.[133] Severity of injury did not correspond linearly to reported memory function. Benedictus[134] recommends using more specific outcome scales to best identify cognitive problems that could negatively impact RTW.[134] The VRC must carefully investigate the allied health professionals' assessment and documentation of cognitive skills and determine the degree to which they will impact job performance. Various jobs have different cognitive demands; for example, the cognitive requirements for professional and technical positions are greater and will require more attention to higher-level cognitive function.[49]

A primary indicator of success may be found in the individual's attention skills. Mateer and Sira relate five components of attention: arousal, sustained attention, working attention, selective attention, and divided/alternating attention.[135] The person must be able to maintain a focus of attention without undue interference or loss of information (sustained attention and vigilance). They must also be able to shift attention readily between two or more activities and do so efficiently without undue delay or loss of information or accuracy (divided/alternating attention). Melamed found that attentional capacity for shifting between dual task performance correlated with likelihood of RTW.[120] Internal distractions can pose a problem for the individual. Techniques, such as thought-stopping exercises and learning to manage one's reactions to error, can reduce internal distractions.[135]

Mateer and Sira suggest that education, rehabilitation, and environmental support can be effective for higher levels of attention, such as sustained attention, working memory, selective attention, and divided/alternating attention.[135] Artman and McMahon also describe helpful environmental supports.[132] These include the following:

1. Reduction of distractions
2. Selection of facilitating environments
3. Reduced visual clutter/use of lighting to improve contrast
4. Posted reminders
5. Labels
6. Message centers
7. Use of external aids (written calendars, smartphones or tablet applications)

These authors also suggest the utilization of task management strategies, such as doing one thing at a time, using earplugs, using answering machines or voicemail to reduce interruptions, and selecting nonpeak activity times to engage in certain aspects of one's work when the activity level of the environment can be expected to be lesser. Other strategies include the following:

1. Pacing
2. Alternating easy and difficult task
3. Taking breaks
4. Slowly increasing the amount of time on a task
5. Taking enough time to finish a task

Metacognitive strategies, such as encouraging the development of awareness of attentional failures and the reasons for them, can be helpful.[135,136] The individual's sense of self-control and his or her ability to manage his or her emotional response may improve with such awareness, positively impacting self-esteem. Ownsworth implemented a 16-week metacognitive contextual intervention with three people attempting to return to work post-TBI.[136] The approach involved group sessions focusing on self-awareness, cognitive strategies, social skills, fatigue management, life/work balance and motivation, individually tailored activities, and home and community sessions to carry over the skills learned. All of the clients who participated in this small study achieved their RTW goals using this approach.

Memory impairments clearly pose great difficulty in RTW. In some circumstances, the individual may not have been given access to or benefitted from cognitive rehabilitation services that resulted in improved memory function. Internal compensatory memory strategies can be effective in that they are always available to the individual. However, they can be limited in effectiveness due to difficulties the individual has in recognizing a need for a particular strategy or difficulty remembering to use a strategy.[135] External memory aids can be considered and may be more pragmatic, depending upon the nature of the information to be remembered or aided. External or environmental supports include the following:

1. Environmental modification
2. Posted lists
3. Labeling
4. Calendars
5. External reminders
6. Aids such as
   a. Alarms
   b. Timers
   c. Beeping watches
   d. Computer-based reminders
   e. Pagers
   f. Cell phones
   g. Key finders
   h. Medication organizers
   i. Smartphone/tablet applications
   j. Voice recorders[137]
   k. Calendars/day planners
   l. To-do lists
   m. Contacts list

In the end, even these techniques can fail due to the individual forgetting to use them, difficulty in operating devices, failure to use a technique systematically, or simple embarrassment.[135] Finally, the creation of task-specific routines can be useful in the form of checklists that enable the individual to be systematically reminded on how to complete a routine in the same manner every time.

Executive function is critical to overall success in return to work. The individual must be able to initiate, set goals,

plan, organize, exercise judgment, and self-monitor and modify plans and/or behaviors according to feedback received.[111,135] The end product of job performance may not be immediately apparent in many vocations in which the work of an individual contributes to a large process and delayed production or emergence of a work product. In these instances, deficits in discriminating response–consequence relationships[138] may impact an injured person's understanding of the impact of a failure to properly execute his or her job responsibilities or his or her ability to identify social cues within the workplace.

Some interest is beginning to emerge in the areas of virtual reality-based cognitive training to prepare people for return to work in a low-risk environment. Man et al. conducted a RCT study using a virtual reality program to challenge work-related skills.[139] He found that the virtual reality program significantly improved a person's cognitive performance on testing, but that the improvements did not generalize into the work environment. The current limitation in the use of virtual reality in work rehabilitation is that it is difficult to individualize the environment to the variety of work duties that patients perform in their respective jobs.

RTW may be most successful in cases in which job performance relies heavily upon previously learned information and skills and in which physical impairments are relatively minor or can be minimized by adaptation of the workplace. Job performance that relies heavily upon new learning or rapid information assimilation will pose far greater challenges to the person with cognitive deficits following TBI. Further detail regarding cognitive function and rehabilitation can be found in Chapters 27 and 28.

Communicative deficits

Some of the more common communicative deficits seen following TBI include oral dysarthria,[140–142] impairments of voice production and volume,[143–147] impairments of the prosodic features of speech,[148] impairments in auditory processing speed and accuracy,[149] and impairments in communicative pragmatics.[150–153]

Oral dysarthria presents with a slurred, thickened speech and can imbue the speaker with unflattering attributes to the uninformed listener. The speaker can appear to be under the influence of alcohol or drugs or can appear less intelligent than is truly the case. Because understanding dysarthric speech requires much more time and effort on the part of the listener, communication on the job may be diminished to unacceptable levels. Couple this with the logical impact on socialization, and a formula for isolation is present. A negative spiral, beginning with difficult communication, can progress to a reluctance to engage in appropriate clarification of details for a job task, reluctance in allocation of job tasks to the injured worker, frustration for the injured worker and supervisor at task failure, and arrival at a conclusion that the injured worker cannot complete the necessary job tasks to maintain employment.

Likewise, other communicative deficits can bring about deterioration of communicative events within a workplace. Inability to engage in communicative pragmatics, such as appropriate conversational turn-taking or maintenance of the topic of conversation among a group of coworkers, will discourage others from approaching and engaging the injured worker in either job-related or social discourse. People with TBI often have difficulty getting the point from figurative or metaphoric expressions, knowing the alternate meanings of ambiguous words, deriving inference, conveying the communicative intent of a speaker to another, and resolution of communicative ambiguity.[154] They will often produce speech that is shorter in length, less complex, and with less cohesion than people without TBI.[155] These tendencies will complicate communication on the job and require attention prior to and after RTW. Understanding the communicative intent of a speaker is heavily dependent upon interpretation of the prosodic nature of the communicative act, and accompanying cues can be found in facial expression and body language. Failure to detect the facial and body language expressions of coworkers or employers often manifests as failure to identify and respect social boundaries. This can have devastating impact on communication and interpersonal relationships. Ability to perceive and remember facial expression has been demonstrated to be impaired in some people with TBI.[156,157]

Any communicative disorder must be considered for the potential to bring about effects upon the workplace as described previously. Disorders of prosody, such as speaking with a monotone voice or speaking too loudly or softly, can cause tremendous confusion of the communicative intent. A person who speaks in a monotone voice can appear disinterested or unmotivated. Speaking too loudly may make it difficult for coworkers or employers to have confidence that the injured worker can handle sensitive issues in an appropriately discreet fashion. The speaker may be confused with being angry or upset when speaking too loudly. Dysfluency or stuttering sometimes occurs following TBI.[158,159] The general public historically misunderstands the dysfluent person, thinking them shy, unconfident, or difficult to listen to. Often, the dysfluent person is reluctant to speak because of the effort required and the embarrassment experienced.

The VRC may be able to impact the workplace by education of the nature of a particular communicative disorder, by adaptation of the workplace, or by encouraging continued remedial therapeutic efforts. Hearing problems may be addressed by medical intervention, amplification, environmental noise reduction, or written communication. In some instances, sign language may be used to some degree. Visual or language deficits may preclude reliance upon written communication, however. As such, graphic skills must also be evaluated for both their potential as a means of expressive communication and as a job requirement for task documentation or interoffice communication. Dexterity may impact the person's ability to write legibly or to use a keyboard for electronic communication.

RTW MODELS

Several models for RTW after TBI evolved in the 1980s, including the *cognitive remediation* model,[113] the *work hardening* model,[160] and the *supported employment* model.[161] Of these models, the most efficacious model appeared to be the supported employment model. In the supported employment model, "job coaches" are assigned to individuals to work alongside the injured worker in the workplace. Their primary function is to teach the job, monitor performance, and provide feedback for the individual and other rehabilitation professionals as to job completion and quality.[162,163] Compensatory strategies may be implemented on the job as identified and designed by the job coach. West et al. describes the role of job coach as having an advocacy component and an active role in job retention by provision of assessment of social skills and productivity.[163] These authors and others[49] suggest that job coaching should be both intensive and of sufficient duration so as to properly ensure both RTW and job retention. Wehman et al. reported that an average of 291 hours of job coaching was used to secure and maintain job placement in a population of people with TBI who averaged 7 years postinjury and 53 days of unconsciousness.[164] Haffey and Abrams reported a mean of only 85 hours per client for job coaching; however, their population was much closer to date of injury.[165] Catalano et al. reported an average case expenditure for successfully vocationally rehabilitated individuals of $4,809 over a much longer program that averaged 27.51 months.[166] Clearly, interventions, such as job coaching, could not have been extensively used. Expenditures appear to have been related to job support, such as counseling, miscellaneous services, and college training costs.

Utilization of job coaching, however, is not without its disadvantages. The injured worker can be stigmatized by the presence of the job coach. It may be difficult to transition the job coach out of the work environment. Last, the job coach may impact the manner in which other employees behave and interact with the injured worker.[167] Consequently, it may be advisable to look for opportunities to use coworkers in a supportive role with the injured worker although care must be taken to properly time the transition from a job coach to a coworker when the relative workload warrants such a change. Alternatives or supplements to job coaching can be "twinning," which involves pairing clients with a key coworker to build confidence prior to returning to work,[168] or on-the-job mentoring.[169]

Wehman et al. reported on vocational outcomes for 59 individuals with moderate-to-severe TBI.[164] Individuals' injuries were classified as moderate-to-severe if coma duration was greater than 24 hours or if GCS was less than 13. Average age was 32.6 years. The majority of individuals had a high school education or greater (76.9%), and 71.4% were employed full time prior to injury, 3.6% part time, and 1.8% were students who also worked. Individuals who returned to work averaged 42.58 months of employment with an average salary of $26,129.74 per year. The average cost of employment services was $10,349.37. Cumulative earnings for the group equaled $1,489,395, and cumulative program costs equaled $491,032.

Some authors suggest that supported employment may not be the most efficient model for successful VR of people with TBI.[170] Models involving job coaches can be costly, reportedly $9,000 to $10,000,[171] and consequently, such services may not be made available to people with less financial support for recovery. As a consequence, less expensive models have been used with the TBI population. These models include the *clubhouse* model,[172] *community-based training* model,[36] and the *empowerment* model.[170]

- The *clubhouse* model uses community-based training and natural supports. "Clubhouses" are "work units" that provide various work samples for clients to identify their particular interests and relative strengths. Support, training, and employment opportunities drive this model. An estimated 18% to 23% of those involved in the clubhouse model ultimately participate in competitive employment.[172]
- The *community-based training* model incorporates supported employment and work adjustment training to address economical disadvantages, job retention, and identification of meaningful and satisfying employment. These programs allow for equal input from the individual, program staff, and training/work site with a RTW plan developed. Individuals obtain work skills in an unpaid work setting. When the employment opportunity begins, the job coach is introduced to assist the person during transition into competitive employment by providing suggestions for work modifications, assistive devices, and strategies for improved work performance.[36] Community-based training models greatly challenge strategy development and enhance the opportunity for generalized work skills.[36]
- The *empowerment* model was designed to consist of several elements sequentially performed to include intake of personal information, vocational evaluation, work samples, work hardening, vocational counseling, job skills training, development of job skills, job training placement, and counseling for continued support.[170] Abrams et al.[170] followed 106 people involved with this type of VR. Within 1 year, 92% were employed, and 24% returned to the previous employment. The authors emphasized coordination of services based on individual need rather than mandatory programmatic requirements for people with TBI.

In a systematic review by Tyerman et al.[173] four models of VR after TBI were described: 1) brain injury programs with integrated or added vocational components. These models emphasize early intervention and integrated RTW preparation into the medical rehabilitation of the patients and provide on-site integrated elements of VR without the involvement of a VRC. 2) VR models adapted for brain injury, involving more traditional VR services (supported employment models and VRC involvement)

for people with brain injury as a part of their rehabilitation. 3) Case coordination/resource facilitation models: This model emphasizes an on-site coordinator to gather and identify resources on-site during their rehabilitation and in the community, including VR services as needed. 4) Consumer-directed approach: This approach involves the clients leading the direction of the RTW process. The clubhouse model described above is the clearest example of this approach. Tyerman found that there is emerging strength of evidence for a clearer need for VR specialist involvement in brain injury rehab, but further, more consistent research is needed. Also, their results indicate that there may not be one best model as described earlier; the needs of the individual should be taken into consideration and model applied accordingly to meet their vocational needs. Fadyl et al. described three models of VR for people with TBI: 1) program-based VR, 2) supported employment, and 3) case coordinated.[174] These models are reflective of those described by Tyerman,[173] and no clear "best practice" among the models was identified.

In a report by Malec et al., the impact of resource facilitation was examined and found to be successful in facilitating RTW.[175] A primary constituent of resource facilitation as described by these authors was availability of early identification of persons needing medical services, medical and VR and facilitated access to personal and community-based vocational counseling services, access to community-based services for supported employment, job coaching, job development and job placement, independent living services, social and mental health services, and comprehensive integrated rehabilitation services in day program formats.[175] The authors report improved vocational outcomes compared to those reported in other studies referenced earlier with the provision of a tremendous array of necessary and useful services. In summary, models of vocational rehabilitation currently in use for people with TBI achieve the best outcomes when they consider the unique challenges of this population and utilize integrative approaches over appropriate time durations and with appropriate supports. As these models become more widely implemented, it will be possible to conduct research to determine whether the programs are less expensive and involve more clients in the VR system and which approaches yield the best outcomes for subgroups of the TBI population.

FORMALIZED VR IN TBI

The literature supports the idea that disincentives for RTW exist and negatively impact RTW rates. Of interest is the idea that RTW is higher for those without such disincentives. The need to work can be financial, social, or emotional. Although workers' compensation benefits often include some provision for VR, accident and health insurance plans have no such provision. So, although VR may be accessible under workers' compensation plans, the individual with private health insurance coverage will require other options. The need to integrate VR services into medical rehabilitation planning and programming and the improved outcomes associated with early versus late vocational interventions creates a dilemma for professionals. It can be difficult to bring about such vocational planning integration and prolonged VR programming as is often required following brain injury. Hence, it may be useful to consider roles to be played by professionals of the treatment team. The scope of practice for occupational therapy includes "work," which encompasses employment-related and volunteer activities. Consequently, it is clearly acceptable for occupational therapy to assist in all processes related to RTW and may serve as an important option in the face of restricted benefits for VRC specifically. The need for integration of VR services provided by public agencies into the medical rehabilitation planning and programming presents yet another considerable challenge to be considered.

Prevocational counseling

Prevocational counseling is a process whereby the client's readiness to return to work becomes an active focus of treatment. The client's readiness and expectations must be reviewed and, perhaps, adjusted. Adjustment to disability can stand as a significant barrier to RTW, especially in instances in which the individual may not be able to return to preinjury employment. It may be necessary to return to a lesser position within an employment setting, a part-time position, or a different position and employer altogether. For some, return to competitive employment may be questionable and only attainable after an extended period of work hardening. Finally, some individuals may be unable to return to work in any capacity or may have sheltered work placement as a long-term outcome. Given the degree to which work impacts self-esteem and self-concept,[101] changes in work status following injury can have tremendous impact upon the individual, his or her family, and his or her social interaction.

In the prevocational counseling process, information is collected regarding historical matters, such as level of educational attainment and achievement. Previous work positions, employers, pay scales, and relevant vocational information are collected. It can be helpful to determine the nature of positions that exist with the employer of injury as well as contacts that family and friends may have. Previous employers can be helpful in RTW, especially in instances in which the person was well regarded. As historical information is collected and considered, it must be combined with information of known or anticipated limitations that may arise due to physical, cognitive, behavioral, psychological, social, communicative, or emotional factors. For example, an individual with an extensive roofing installation background who has vestibular and visual deficits is unlikely to return to roofing installation. However, the person's extensive knowledge base may facilitate work in the roofing field as an estimator, sales person, or supervisor.

Vocational evaluation

Stergiou-Kita et al. undertook a systematic review of the literature in vocational evaluation after TBI and provide a useful framework of overarching guidance in seven key processes.[176] These processes consist of 1) identification of the purpose and rationale of the evaluation, 2) intake process, 3) assessment of the person, 4) assessment of the environment, 5) assessment of the occupation/job requirements, 6) analysis and synthesis of assessment results, and 7) development of evaluation recommendations.

The evaluation will set the tone for the balance of the VR processes and has the greatest impact on the likelihood of a return to vocational involvement. Vocational evaluation should consider not only the abilities and aptitudes of the individual being assessed, but must also consider important factors about potential jobs, workplace characteristics, coworkers and employers, and financial incentives and disincentives to returning to work. Vocational evaluation cannot be conducted in a void of substantial interaction with other allied health disciplines that will have contributed to an individual's recovery. These professionals can provide extensive insight into skills, aptitudes, environmental concerns, and methods of adaptation to RTW barriers. In fact, VR may be ultimately undertaken by disciplines other than VRC.[177]

VR plan development

The vocational plan begins during the prevocational counseling process as the counselor attempts to piece together options for the various phases of return to work that may be necessary for the client. Requisite phases will vary from client to client. In many instances, development of a formal VR plan will be required for submission to workers' compensation agencies or other funding sources for approval. In others, the formal VR plan and all the attendant filing of forms may not be needed. Nonetheless, the formal VR plan is integral to the process of returning an injured worker to work.

Plans developed for different individuals will vary considerably in the amount of time needed, the cost, and the process owing to the tremendous individuality of each person with TBI. The plan must be developed in congruence with the interests, goals, aptitudes, and abilities of the injured worker as well as consideration of the labor market and job availability. Ninomiya et al. developed a list of issues that should be considered during the development of a rehabilitation plan.[178] These items are as follows:

- Actual versus stated motivation for the client's RTW
- The individual's cognitive abilities
- The individual's emotional profile
- Physical deficits and limitations
- Family support and interactions
- Financial gain or need
- Litigation
- Self-esteem and self-concept
- Work ethic
- Work history
- Preinjury work characteristics
- Current and preinjury personality factors
- Adjustment to disability
- Transferable skills
- Age
- The general employment index in the geographical area of the intended discharge
- Employer prejudices regarding brain injury and other disabilities
- General medical stability
- The presence or absence of a seizure disorder or other neurological deficits
- Potential areas of conflict arising from various secondary gain issues

Vocational plans traditionally encompass one of the following seven outcomes: *RTW, modified work, alternative work, direct placement, on-the-job training, formalized schooling or training*, and *self-employment*. The order listed suggests a hierarchy of desirability. The *RTW* outcome is achieved when the injured worker returns to his former employment, in the same position, with the same number of hours, and at the same workplace. A *modified work* outcome consists of a return to the former employer although modifications have been made to the work process or work station to accommodate for physical, cognitive, or other limitations. An *alternative work* placement also occurs with the former employer although the injured worker is placed in a different position altogether. The new position may have been identified via transferable skills analysis and is consistent with any limitations. *Direct placement* consists of a new position with a new employer or a similar position to the position of preinjury employment, again using transferable skills. *On-the-job training* occurs with a new position and a new employer. The employer provides a training environment and some or all of the training. Responsibility for compensation can be shared between the employer and a workers' compensation carrier. Insurance or employer benefits may continue until a successful long-term placement is assured. *Formalized schooling or training* plans involve enrollment in a vocational or academic schooling setting for the purpose of achieving vocational placement upon completion. The *self-employment* outcome is used when the plan is to establish a new, independent business that the injured worker will operate. Each of these plans assumes a competitive employment outcome. Occasionally, during execution of a plan, the VRC and injured worker may determine that the plan is not going to be successful. They may opt to modify the rehabilitation plan and establish a different outcome as the goal of the new plan.

The VRC will need to explore creative vocational options with the client, the employer, and family and friends as well as medical rehabilitation providers. The process can require great diplomacy and careful planning. Although

many employers are eager to be helpful in returning an individual to work, there may be other circumstances in which the employer is less willing. For example, the individual may have had a poor work record or may have been injured shortly after hiring. He or she may have been difficult to get along with. The employer may be fearful of reinjury or customer reaction to the injured worker. Some employers are angry with injured workers for either the damage done to themselves or others or for the financial losses incurred. Conversely, employers can be unrealistically optimistic about the person's recovery and, in their efforts to be supportive and encouraging, promote an RTW that is neither likely nor reasonable.

Care must be taken to avoid premature RTW or RTW that is ill-suited to the person's skills. A well-meaning family, employer, medical rehabilitation provider, or client can bring about an RTW that is doomed to failure due to poor matching of the job requirements and the person's residual and recovered skills. Vocational failure brings about embarrassment, humiliation, disappointment, and withdrawal of support. The employer of injury may represent an excellent final job placement but a poor initial work-hardening placement. The employer of injury and coworkers have intimate knowledge of the injured worker. Despite the best preparation, these parties will often be quite surprised at the differences they find in the injured worker. Their reaction may be so profound as to cause fear about safety, doubt about recovery, and reluctance to allow sufficient time and opportunity for progression through an extended work hardening, on-the-job training, and job coaching process before arriving at a final job placement. The injured worker, too, may be keenly aware of colleagues' watchfulness, and the extra social pressure can be unduly difficult.

Consequently, the prevocational counseling process should include an orientation for the client and family as to these potential pitfalls. The plan should evolve to identify and avoid as many of them as possible. Education regarding the prolonged nature of vocational intervention and description of the process as a "therapy" rather than job placement can be helpful in arriving at a good understanding of the need to effect appropriate opportunities for transition into the RTW process.

Once a vocational plan is established, it is often necessary to educate financially interested parties as to the need to follow a protracted VR course for people with TBI because most claims adjusters and case managers will have little experience with TBI. Their usual experience with VR will be such that they will expect a comparatively short and simple process. They may expect that the medical file be closed and the client determined to be "permanent and stationary" (P&S) or at "maximum medical improvement" (MMI) before allowing formal VR involvement. As has been discussed earlier, it is imperative in TBI that vocational and medical rehabilitation be better coordinated early in the recovery process. Determination of P&S or MMI status can be made shortly before final job placement and need not precede the commencement of VR.

The VRC must evaluate the degree of awareness the medical rehabilitation professionals have regarding the likely job requirements for which they must attempt to prepare the injured person. The counselor may choose to develop job requirements for several possible job descriptions and meet with medical rehabilitation staff to review the position demands. Medical and therapeutic planning can be quite different when knowledge of such requirements is introduced. These differences can range from alteration of timing for various elective or planned surgical interventions to whether or how long therapy continues and to what goals.

VOCATIONAL COUNSELING

The VRC should begin VR counseling with adequate disclosure of each party's roles and responsibilities. Expectations for the vocational process should be evaluated and clarified. Most people do not have a clear idea as to what VR entails, and so it is quite important to undertake a clear discussion of what is expected of the injured worker, an employer, and the VRC. Most states have requirements for provision of VR benefits. Some insurance carriers and some states have published materials that explain available benefits to the injured worker. Because memory function may be impaired, it may be advisable to include a family member in the discussion of benefits to be sure that all their questions are answered and that the information can be reliably presented to the injured worker in case aspects of the discussions are forgotten. Provision of available benefits in writing can facilitate this process.

The VRC may face obstacles posed by misinformation that an injured worker or his or her family has obtained from friends or family who had experience with VR for a different injury or in a different state. The existence of such experience should be actively investigated as it will most likely influence receptivity to VR.

The VRC must learn the vocational goals and expectations the injured worker and his or her family have. There may be discordance within a family or between the injured worker's desires and his or her abilities. Vocational counseling should undertake a supportive and coordinated educational process to attempt to align expectations and goal setting from the outset and before progression on the plan. The VRC will need to include medical rehabilitation professionals, case managers, claims adjusters, attorneys, and staff of state departments of VR in these discussions to arrive at a VR plan that has attainable goals that are agreed upon by all interested parties. Given the large number of interested parties and their respective roles, reaching concordance is crucial although difficult.

Assessment of dependency must be undertaken in the vocational counseling process. Dependency can take many forms and is fostered, to some degree, through the medical rehabilitation process. The injured worker may need some assistance in overcoming learned dependence and moving toward independence and self-reliance once again. Dependency can be psychological, financial, social,

or medical in nature. Psychological dependencies include having learned to be more comfortable having things done for one, rather than doing for one's self, having developed a dislike of a particular job or distrust of an employer, deriving some emotional benefit from medical treatment or the disabled status, or having developed a fear of failure that precludes consideration of reentry into the workplace as an independent person. Financial dependence can include the idea that it is easier not to work than to work for a minor discrepancy in income, income stability due to regular income payments rather than income derived from seasonal work, or acceptance of the idea that injury deserves compensation even though a Social Security or workers' compensation payment is not designed as such. Social dependency can occur when immigration status is dependent upon medical status or when cultural mores are such that injury is viewed as permanent and, consequently, as an entitlement rather than as something that is temporary and amenable to change. Medical dependency can include substance abuse that may or may not have preceded the injury.[179,180] Once dependencies and their etiologies are identified, the VRC can work with a counselor or psychologist to address the dependencies and attempt to reverse them. Some dependencies, however, will not be amenable to reversal, and VR plan success will be negatively affected.

VOCATIONAL TESTING/WORK EVALUATION/WORK HARDENING

A thorough vocational evaluation is of paramount importance to achieving return to employment. An evidence-based framework for vocational evaluation following TBI was developed by Stergiou-Kita et al.[181] to provide recommendations for best practice in vocational evaluation. They identified seven key processes, including 1) evaluation of the evaluation purpose and rationale, 2) intake process, 3) assessment of the person, 4) assessment of the environment, 5) assessment of the occupation/job requirements, 6) analysis and synthesis of assessment results, and 7) development of evaluation recommendations. This comprehensive evaluation includes looking at prognostic factors and the full aspect of the ICF model to generate an optimal plan and is now a clinical practice guideline.[176]

One frequently underestimated aspect of the assessment of the patient is their subjective experience and investment in the vocational evaluation process. Hooson et al. found that engaging in an RTW process can be emotionally very difficult for people with TBI and that people experience a grief reaction when returning to work as they start to integrate their preinjury employment status with a different set of abilities postinjury.[2] Clients report needing to feel respected in the process and work with those who are adaptable and invested in their individualized goals. They found that programs that involve family members and caregivers closely can help establish long-term support and follow up for long-term success. Stergiou-Kita et al. also emphasized the need for a client-centered approach to evaluation.[182] They found that evaluators should 1) determine the meaning of work to the client preinjury and assist in determining new meanings as needed, 2) recognize that a new identity is being formed in the RTW process and support emerging self-awareness, 3) provide opportunities to try and take potential risks, and 4) assess the supports available to the client and work toward building depth in long-term support. Keeping the client at the center of the evaluation process can assist in maintaining longer-term investment and motivation, therefore making room for vocational success.

In addition to the subjective aspects of the client, more objective measures of assessment of the person can include interest inventory testing, vocational aptitude testing, utilization of standardized work samples, and utilization of work samples to assess specific skills. Many interest inventory and vocational aptitude tests are commercially available.[165–167,170–172,178–180,183–187] These tools are often helpful in identifying alternative employment options that may be of interest and within the capabilities of an injured worker who cannot return to the preinjury employment. Results of these tests facilitate discussion and exploration of vocational options although some care must be taken in that the universe of options is opened to the individual. This can be problematic as some options may require an extended vocational or educational training that is not practical. Similarly, some options may entail self-employment. Given the nature of limitations experienced following TBI, formalized schooling and self-employment plans are less likely to be successful. In fact, it has been demonstrated that formalized schooling plans in VR with other populations are less successful than nonschooling plans.[188]

Assessment of the workplace involves looking both at the physical environment and the social demands of the environment. Ellingson and Aas[189] found that the most significant environmental barriers of the workplace in RTW were high workplace demands, the adjustment of employers and colleagues, complicated information and bureaucracy, physical barriers, and too little practice prior to returning to work. In contrast, they found that more social support, understanding from the employer, and low physical barriers were helpful in facilitating RTW. They found that more thorough assessments also facilitated a successful RTW. In addition, personal factors were examined in this research. Stergiou-Kita et al. identified four primary workplace factors influencing RTW: 1) workplace demands, 2) employer risks and burden, 3) risks associated with information sharing, and 4) financial implications associated with RTW.[190]

Vocational evaluation may require a protracted timeline to properly complete.[191] Work evaluation consisting of situational[86,191] or community-based assessments, functional evaluation, simulated work, and work samples[192] might be included to identify potential barriers to employment that may not have been identified. Work evaluation can be helpful in determining whether a work adjustment or work-hardening experience is warranted. Standardized work samples can be used that allow comparison of the person's

function with a normal population. These work samples can be used to evaluate ability to use small tools, size discrimination,[193] numerical sorting,[194] upper extremity range of motion,[195] clerical comprehension and aptitude,[196] independent problem solving,[197] multilevel sorting,[198] simulated assembly,[199] whole body range of motion,[200] trilevel measurement,[201] eye–hand–foot coordination,[202] and soldering and inspection.[203] Work samples designed to assess specific work skills can also be derived from an employment setting. Information is collected about the usual method of completion, time to complete, and job outcome, which is then compared to the skills demonstrated by the injured worker.

Work hardening placement is used to develop physical, cognitive, social, and job skills for a specific position although the plan might intend that those skills will ultimately transfer to other job placements. Strength and endurance can be gradually improved by using a graded number of hours per day for the work schedule. An advantage to a work hardening placement is that it is disposable. That is, mistakes made on this type of placement can be used as learning experiences and are not likely to be noted by friends and coworkers. Gradual improvement in work productivity is the key to work hardening placement. It is sometimes useful to utilize more than one work hardening placement due to information gleaned from the first. The individual may demonstrate skills or a lack thereof that were not identified during testing.

Accommodation to the workplace and all its demands can be accomplished by transition built into the work schedule and work responsibilities. Development of positive worker characteristics is an early focus. Continued monitoring by the VRC or job coach can provide excellent information to therapists for additional emphasis on identified areas or for compensatory approaches to be developed. The VRC must ensure that the work hardening experience provides good feedback to the injured worker and work to maintain an employer's willingness to continue to provide access to the work hardening setting. Work hardening experiences need not be paid positions in order to be valuable. Some people benefit from protracted volunteer experiences, gradually improving endurance, positive worker characteristics, and job skills. On the other hand, work hardening experiences may progress within an employer's setting and culminate in an actual job placement. Obtaining a job placement from an initial work hardening experience may be as dependent upon the VRC's management of the entire process as it is upon the injured worker's skills and progress.[34]

The VRC must be certain to file all appropriate paperwork on behalf of the injured worker, insurer, or employer, as required by law. Continued monitoring of progress in medical rehabilitation occurs until the proper time for administration of prevocational counseling and vocational testing is identified. As the injured worker nears completion of the medical rehabilitation plan, vocational evaluation begins.

As the medical rehabilitation process winds down, part-time work hardening placement or situational assessment can be used to reintroduce the injured worker to the workplace and assess and reestablish good basic worker characteristics, such as appropriate dress, punctuality, and job task completion. Work hardening placement may be progressive in the amount of time spent on the job, in the nature of the work undertaken on a given job, or in changing from one job description to a more demanding one. Extensive job coaching should be used in the work evaluation and work hardening processes.

Success in work hardening placement(s) leads to job placement in what may become the final placement for the injured worker. Job coaching should continue as needed and be transitioned out of the job site according to success. Continued monitoring should be undertaken for 6 to 12 months before case closure is achieved. Sale et al. reported that placements often failed due to a number of events occurring on the job rather than a single event, suggesting a role for VRC intervention.[34] Finally, the VRC should always compare the original vocational goals and predicted vocational outcome with the final achievement to attempt to derive ways of improving personal effectiveness.

To summarize, in the general course of VR for TBI, the VRC enters the process by monitoring the medical rehabilitation status and progress. A job analysis and description of the employment at the time of injury should be obtained and shared with the medical rehabilitation team. Likewise, a work history that reviews all past employment should be collected and shared. As this information is considered, the VRC and medical rehabilitation team can begin to discuss the RTW process and bring about the establishment of appropriate expectations for RTW among themselves and with the injured worker and family, review prognostic variables that may impact RTW, and review funding options and programs that will be available.

FOLLOW-UP

The role of follow-up cannot be overstated. Given the instability in job maintenance following TBI, planned follow-up conducted over a lengthy period of time is only logical.[20, 204] Unfortunately, however, completion of follow-up activities requires the approval of the client, the employer, and possibly an insurance carrier in addition to the willingness of the VRC. Objectives for the follow-up visits should be clearly delineated in advance with all interested parties as part of the VR plan.

The primary purpose of follow-up is to determine whether the individual is experiencing any problems on the jobsite that can be rectified before they culminate in job separation. The injured worker may or may not be aware and forthcoming about problems as may be the employer.

The VRC must consider tardiness, absenteeism, social interaction, and task completion at a minimum. Careful interview with the injured worker, family, coworkers, and the employer may reveal small or emerging problems that can be addressed. The VRC should review current job duties

and compare with original responsibilities. Any changes that are noted should be reviewed to determine if they are compatible with known skills and aptitudes of the injured worker. Boots and Chapparro described the unique use of a tool used to evaluate and treat people with multitasking difficulties in the clinic in a case study on the job.[205] The Perceive Recall Plan and Perform (PRPP) system of task analysis was adapted for on-the-job work assessment with input from the employer. Using the PRPP-Work, the employer could assist in rating the client, resulting in improved insight of the client and the employer.

The VRC must also investigate whether events have transpired that might jeopardize placement that may not be work-site related. These include motor vehicle infractions or accidents, hospitalization, substance abuse, family or marital discord, or failure to comply with prescribed medical or therapeutic treatment plans. It may be advisable to contact the local department of motor vehicles (DMV) to check for infractions, accidents, or substance abuse.

The VRC must collate the collected information at follow-up and determine the manner to best approach addressing identified areas of concern. The goal must be to conduct follow-up frequently enough so as to allow early identification and resolution of problems, thereby ensuring job retention. Follow-up should be supported over an extended period of time to optimize RTW outcomes.[177]

SUMMARY

Successful VR represents, perhaps, the highest achievement of return to life to be achieved after TBI. Formal VR is challenged by societal predispositions that often preclude the initiation or successful completion of such efforts. The process is extremely complicated and requires a thoughtful, adaptable, and progressive approach to restoration of the ability to work. Stability of medical rehabilitation outcomes and overall life satisfaction can be positively impacted by collaboratively undertaking the hard work involved in returning a person with TBI to work.

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PART 4

Case management

31

Contribution of the neuropsychological evaluation to traumatic brain injury rehabilitation

JAY M. UOMOTO

INTRODUCTION

Neuropsychological evaluations are an integral part of neurorehabilitation service delivery. The contribution of neurocognitive and neurobehavioral data adds to that obtained from physicians (e.g., physiatrists, neurologists, primary care physicians), nursing staff, speech pathologists, physical therapists, occupational therapists, therapeutic recreation therapists, case managers, social workers, and vocational rehabilitation counselors. Neuropsychological results on a person with traumatic brain injury (TBI) of all levels can be applicable to all disciplines involved in comprehensive rehabilitation care given that the consequences of TBI are cognitive, behavioral, interpersonal, and physical in nature. Therefore, the major purpose of this chapter is to provide an overview of the purpose, scope, and implications of neuropsychological findings in those with TBI.

Historical context of neuropsychology

Throughout history, the centrality of comprehensive assessments of those with acquired brain injury has been emphasized and provided the foundation to defining rehabilitation strategies that can be applied to the individual with TBI. An example of one of the earliest comprehensive accounts of the physical, neurocognitive, and neurobehavioral consequences of acquired brain injury was penned by renowned neurologist Kurt Goldstein[1] in his book published in 1942, *Aftereffects of Brain Injuries in War.* Much is often learned, tragically, from injuries sustained by military service members in combat. In his book, Goldstein described characteristic symptoms of those with acquired brain injury based upon his clinical experiences in monitoring and treating numerous patients after combat, some over the course of 10 years. Goldstein observed precise insights regarding the

scope and genesis of disorders of motor output, sensory input, visuospatial, brain stem, and frontal lobe functions. His neurological insights converged with his methods of assessment of cognitive functions and impairments and described his approach to what would today be considered elements of the neuropsychological evaluation.

According to Goldstein, these assessments were conducted for the following reasons:

- To evaluate some of the mental functions usually separated in psychology, such as memory and attention.
- To evaluate the patient's general level of performance. Some mental and physical performances are investigated over a period of time. The results obtained here are also useful for our judgment of the subject's capacity in general.
- To ascertain the circumscribed mental defects, in detail, as a basis for procedure in retraining.
- To study the subject's working capacity in special kinds of labor. (p. 92)

It is important to observe that what Goldstein termed *psychologic laboratory examinations* are very similar to what can be seen as the essential goals of the neuropsychological evaluation in the context of TBI rehabilitation. These goals are defined as 1) comprehensively delineating the cognitive impairments, preserved abilities, and cognitive assets that have resulted from TBI; 2) relating the neuropsychological profile to correlate with and predict a patient's overall functional capacities; 3) utilizing neuropsychological findings to inform rehabilitative therapies; and 4) integrating neuropsychological insights into the larger goal of improving quality of life, including return to work, school, and community reentry.

Origins of the term "neuropsychology"

The use of the term *neuropsychology* is often attributed to Sir William Osler[2] in an address to the Phipps Psychiatric Clinic at Johns Hopkins Hospital in 1913. During this address, Osler underscored the importance of paying close attention to the interactions between brain function and psychiatric disorder in clinical medicine. Although this term largely lay dormant for decades thereafter, Osler's comment portended what has become characteristic of modern neuropsychology. Here, this same convergence of physical and psychological realms defines the field as the study of brain–behavior relationships.[3]

Kurt Goldstein's early work in describing and rehabilitating individuals with acquired brain injury anticipated the view of examining multiple neurocognitive and personality domains as a part of the analysis of brain–behavior functioning. He and his colleagues[4] described a case of a person who sustained a severe TBI in a motor vehicle accident, known as "Case Lanuti." This extensive case study describes this person with TBI as having physical deficits (e.g., loss of facial sensation, muscular weakness, balance difficulties, headache, back pain, presumably visual field defects) as well as neurobehavioral problems, such as irritability and hallucinations. The authors open their article by discussing the relevancy of John Hughlings Jackson's hypothesis that "…mental disorder caused by damage to the brain cortex is not a conglomeration of unrelated defects, but an expression of systematic disintegration" (p. 1). Such clinical conceptualization was consistent with Goldstein's long held perspective regarding holistic neurorehabilitation. In describing Case Lanuti, the authors go on to delineate key neurological areas of concern for the patient. These include *recognition of the environment* (whereas today we might be concerned about visual stimulus perception, visual agnosia, or problems in semantic memory on a confrontational naming task). Case Lanuti illustrated problems with *spatial organization* (what we might call visuospatial analysis, right–left confusion, visuoconstruction), and *use of symbols* (in modern neuropsychological parlance, aspects of language functioning, including expressive and receptive skills, reading and writing abilities, and knowledge of numbers). *Memory* functions are discussed in this case, in which both episodic and prospective domains were illustrated. Also described were the patient's reactions to experiences of successes and failures at tasks from the point of view of *values* (i.e., the expressions of "good," "nice," and "no good" [p. 53]). Today, we might refer to this domain in terms of mood, coping, experiences (or lack thereof) of self-efficacy, and the experience of suffering. In describing Lanuti, they found him to have trouble distinguishing between reality and fantasy (p. 60), which corresponds to our understanding of delusional thinking and hallucinations. The authors also describe the psychosocial consequences of Lanuti's brain injury. Having been hospitalized for 9 years, over time, visits from family members became less frequent, noting that when he went home for visits "…Lanuti did not participate in the life of the family, did not display initiative in social contacts or any understanding of what was going on…" (p. 65). Sadly, the authors surmised that the lack of participation with the family was observed to also be a change in attitude on the part of the family. They were challenged in their ability to cope with the changed person of Lanuti after brain injury. The case, although tragic, yet relevant today, does well illustrate the interactions between physical, neurocognitive, and neurobehavioral aspects of brain injury whereby one could say that the *whole brain impacts the whole person*.

More than 40 years ago, Aleksandr Luria[5] spoke of the integrated nature of higher cortical functions that formed the foundation of view of brain–behavior functioning and rehabilitation, long before the advent of functional neuroimaging technology that, at least in part, confirmed his way of thinking:

> …mental functions, as complex functional systems, cannot be localized in narrow zones of the cortex or in isolated cell groups, but must be organized in systems of concertedly working zones, each of which performs its role in

> complex functional system, and which may be located in completely different, and often far distant, areas of the brain. (p. 31)

The neuropsychological evaluation can be critical to defining plans of care in executing effective neurorehabilitation therapy for those with TBI based on a holistic understanding of brain–behavior functions. Advances in neuroimaging techniques, prospective outcome research, gains in the understanding of the neurobiology of cognition, and movement toward unlocking the mysteries associated with neuroplasticity have enhanced the practice of neuropsychology in TBI rehabilitation. The neuropsychological evaluation provides the clinical data necessary to define both the neuropsychological and neurobehavioral consequences of TBI.

NEUROPSYCHOLOGICAL EVALUATION PROCESS

The practice of neuropsychology continues to change, often in response to the demands and constraints of the health care industry. Although the longer, full-day neuropsychological battery approaches still occur (particularly in the forensic neuropsychology realm), in everyday hospital, medical center, and agency-based practice, more abbreviated neuropsychological examinations are being conducted. Often this is driven by third-party payer limitations, volume of referrals, nature of the referral question, and neuropsychological practice preferences. Current neuropsychology training programs at the postdoctoral residency level may also affect burgeoning practice preferences. That said, the remainder of the chapter is devoted to the larger parameters within which a variety of neuropsychological assessment approaches are conducted. The general philosophy regarding the idea of testing versus evaluation, the typical domains that are covered within a neuropsychological evaluation (whether in a larger more fixed battery approach versus a flexible/abbreviated approach), and a description of the types of tests that are administered in each domain are discussed.

Neuropsychological testing versus neuropsychological evaluation

Before discussing the variety of neuropsychological evaluation approaches and test procedures, it is important to differentiate the process of *evaluation* as opposed to the technical aspects of *testing*. *Testing* refers to only one aspect of the examination, usually the actual standardized administration and scoring of a set of neuropsychological tests. Testing is performed by professionally trained individuals, most often by neuropsychologists and rehabilitation psychologists because neuropsychological assessment is explicitly stated as a competency in each of these specialty disciplines (see the American Board of Professional Psychology[6] for a listing of core competencies). In some settings, speech pathologists will administer a limited set of neuropsychological tests (particularly in the language domain). Neuropsychological testing is performed by the neuropsychologist or by a technician who has been trained in the standardized administration of an array of neuropsychological tests, often referred to as a *psychometrist*, *neuropsychometrist*, or *psychology technician*. Many neuropsychologists elect to administer their own tests when firsthand observation of the qualitative aspects of the patient's performance may be deemed important. The skilled neuropsychometrist is trained to make qualitative observations during the testing process and collaborates with the neuropsychologist for the interpretation of these observations.

Evaluation, on the other hand, refers to the comprehensive and integrative *process* of evaluating the patient and includes multiple sources of input. Sources include review of medical records, patient interview, informant interview(s), performance-based measures (neuropsychological tests), paper-and-pencil questionnaires (e.g., personality questionnaires, postconcussion symptom inventories), direct observation of the patient in the testing setting and in real-world settings, and information gathered upon feedback of testing results. The evaluation process begins at the very first contact with a referral source or with the patient and is concluded when feedback is provided to all interested parties and a report is completed.

Components of the neuropsychological evaluation

Table 31.1 describes the various components involved in the neuropsychological assessment process. Not all components are necessarily included in every neuropsychological examination. The neuropsychologist may employ various components depending upon the referral question. Observations made by rehabilitation team members, family members, coworkers, and other collateral resources may also hone the content of the neuropsychological evaluation. These components comprise an in-depth examination of the patient that covers a broad range of brain–behavior relationships. In the context of brain injury rehabilitation, the neuropsychological assessment provides an active ingredient to planning interventions and defining cognitive rehabilitation strategies that may be executed by the interdisciplinary rehabilitation team. The neuropsychological assessment becomes this active ingredient due to the fact that information regarding deficits will, oftentimes, define the obstacles that potentially interfere with the patient's benefit from rehabilitation therapy. For example, if a patient evidences marked recent verbal memory impairment, verbal instruction alone to complete a set of exercises prescribed by the physical therapist may be problematic. Further, the patient may have trouble recalling the proper sequence of steps for completing an exercise or activity of daily living. Knowledge of the type and extent of the verbal recent memory problem will be useful to the therapist in order to adjust the method of therapy delivery. The therapist may decide to pair verbal

Table 31.1 Components of the neuropsychological evaluation

Component of the evaluation		Comment
1.	First contact with referral source	Ascertain questions to be answered by the assessment, shaping the referral question to best respond to a consultation request. Begin determination of the assessment approach and define other data that may be of assistance for completing the evaluation.
2.	First contact with patient, family, employer, or other party	Understand the patient's and family's conceptualization of TBI relative to the need for the assessment; examine discrepancies between the patient's insights regarding the TBI versus family/friends' view; align expectations between provider, referral source, and patient/family/employer/other of what will be accomplished by the examination. Obtain information regarding preinjury medical, academic, psychological, and psychosocial status.
3.	Medical record review post-TBI	Examination of early records, including field observations of the patient (e.g., Glasgow Coma Scale scores, EMT observations, observer observations, if available); emergency room observations of retrograde amnesia, loss of consciousness, posttraumatic amnesia to assist with grading severity of TBI; evidence for early behavioral agitation; tracking the chronology of events postinjury, including medications, treatments, neurosurgical interventions, medical complications and co-occurring conditions; progression of the symptom complex; rehabilitation therapy; and patient and family response to the rehabilitation process.
4.	Other record review	Examination of educational records to assist with determination of preinjury cognitive and intellectual functioning level, history of psychiatric impairment, mental health service utilization and substance abuse, determination of premorbid neuropsychological risks or condition, preinjury medical history and service utilization that may be contributory to the current evaluation.
5.	Pre-interview questionnaires	Background information may be ascertained on demographics, logistics, medical history, psychological history, notation and rating scales of past and current symptoms, educational attainment and performance; provides information to structure the clinical interview. Examine for discrepancies between self-report and informant reports, record review, and set agenda for seeking potential resolution of inconsistencies during clinical and informant interviews.
6.	Clinical interview–patient	Review medical and psychosocial history, ascertain current symptom complex from the patient's point of view; assist in determining congruency with early head injury severity indices; determine awareness of neuropsychological and neurobehavioral deficits; assist with ascertaining the patient's experience of quality of life post-TBI; obtain observational mental status functioning; determine contributory conditions to cognitive dysfunction, including depression, anxiety, anger/irritability, fatigue and sleep disturbance, pain symptoms and progression, substance use/abuse, medication (prescribed and over-the-counter medications and supplements), use/abuse/polypharmacy. Determine provisional co-occurring psychiatric diagnoses.
7.	Clinical interview–informant(s) (family member, friend, teacher, coworker, employer, etc.)	Review variables mentioned above for the clinical interview with the patient to examine for congruency of that information and obtaining further details; obtain information to judge premorbid compared to post-TBI functioning; assist with the alignment of expectations for treatment and recovery of function in the patient.

(*Continued*)

Table 31.1 (Continued) Components of the neuropsychological evaluation

Component of the evaluation		Comment
8.	Neuropsychological testing	Administration of neuropsychological tests by the neuropsychologist (or other trained and licensed health care professional) or psychometrist (a person trained in the standardized administration of neuropsychological and psychological tests). The length of the examination varies, depending upon the referral question; can extend from a brief mental status examination to a full day or two of testing. Interspersed with actual testing are rest breaks and a break for a meal if completed during the day. Development of interpersonal rapport and therapeutic alliance during standardized administration is key to obtaining maximal testing results. Testing may involve administration by both the psychologist and/or psychometrist and computer-assisted administration of tests. Validity testing (determination of effort and symptom enhancement) may occur near the beginning of the testing session and/or interspersed throughout the testing session. Administration of psychological tests of mood, personality, pain perception, sleep, coping, quality of life, and functional outcome measures (for activities of daily living; instrumental activity of daily living).
9.	Test scoring and interpretation	The neuropsychologist and/or psychometrist scores test protocols; computer scoring programs may be employed; generation of test score summary sheets. Behavioral observations of test administration are recorded to assist in determining validity of obtained test scores. Depending on the outcome at this stage, further testing may be ordered to clarify or expand certain domains that are assessed.
10.	Report generation	A comprehensive report is generated that incorporates the above information; referral questions are answered within the body of the report. A listing of recommendations along with time frames and sequence of importance may be included. Some neuropsychologists may elect to delay the completion of a comprehensive report until after the feedback session in order to include information obtained during that session. Report length is frequently determined by the referral question and context (e.g., medical center–/hospital-based reports may be shorter in length than forensic neuropsychological evaluation reports). Reports may be written for specific audiences, including referring physicians and health care providers, school settings, attorney and forensic settings, case managers, vocational rehabilitation counselors, etc.
11.	Feedback session	Feedback regarding the results of the examination is explained to the patient, family member(s), or others, together or separately. Modification of the report may occur depending upon new questions that may arise; recommendations are made to the patient and family; other providers may be invited to the feedback session, depending upon clinical need and with the permission of the patient; feedback may be provided to case managers, vocational counselors, educational specialists, or other health care providers. Verbal and written feedback to referring sources may accompany the delivery of the report.

instruction with visual demonstration of the exercise set and provide the patient with pictures of the steps of an exercise routine. Breaking a complex set of steps down into component parts and training by procedural mastery and repetition of the ADL sequence may be necessary based on this information about verbal memory impairment. To fully understand a patient's memory capacity, both in terms of assets and deficits, many of the components above are necessary for the accurate determination of that patient's memory abilities. Utilizing deficit information (what constitutes the patient's cognitive limitations or vulnerabilities) paired with preserved and asset information (abilities that remain intact and those for which the patient may excel and capitalize upon) provides significant information to rehabilitation therapists in crafting an effective approach to their intervention. It is in the application of the neuropsychological test findings to the care of the TBI patient that the assessment becomes a powerful instrument to improve the functional status of the patient.

Neuropsychological evaluation approaches

A number of training programs and subsequent models of neuropsychological assessment has emerged since the

beginning of clinical neuropsychology. Often related to a particular researcher or research program, an array of approaches to the neuropsychological evaluation is currently represented in clinical practice. All have been applied in brain injury rehabilitation and have provided an active ingredient to the process of recovery of function in TBI. An early survey of neuropsychological test usage, neuropsychology battery choice, and theoretical orientation found specific clusters of usage.[7] Identified clusters included *fixed-battery*, the *Arthur Benton Laboratory orientation*, *process approaches*, hypothesis-testing approaches, and *eclectic* usage of tests. It is more widely accepted that the quality of the neuropsychological examination is more a function of the training and experience in researching or working with TBI and experience in applying sets of neuropsychological tests with this population. For purposes of brevity, approaches can be grossly divided into *fixed-battery* and *flexible-battery* approaches with exemplars that are not meant to be exhaustive in listing. Further, the remainder of the chapter refers to adult neuropsychological evaluation as pediatric and adolescent neuropsychological evaluation of TBI is beyond the scope of this particular chapter.

FIXED-BATTERY APPROACH

The fixed-battery approach refers to the administration of a uniform set of neuropsychological tests across all patients evaluated. This provides for a systematic comparison of patients across the same sets of tests. The fixed-battery approach usually incorporates tests that cover a full range of brain–behavior functions, including sensory–motor, language, attention and concentration, memory, visuospatial, information processing speed, and executive functioning domains.

Having one of the longest-lasting histories among the fixed-battery approaches is the *Halstead-Reitan Neuropsychological Test Battery* (HRNB) for adults.[8] A child version of the HRNB also has been published although it is now in less frequent use. First developed by Ward Halstead in 1947 to be a measure of "brain intelligence"[9] and later modified by Ralph Reitan in 1955, the HRNB consists of several core tests: Category Test, Tactual Performance Test, Speech Sounds Perception, Seashore Rhythm, Finger Oscillation (Finger Tapping) and Grip Strength, Trail Making Test, Aphasia Screening Examination, Lateral Dominance, and the Reitan-Klove Sensory Perceptual Examination. It can generate the Halstead Impairment Index that provides a gross indication of impairment severity. A General Neuropsychological Deficit Scale can also be calculated from the HRNB (plus other measures) that provides indications of level of performance, pathognomonic signs, pattern analysis, and lateralization indicators. Other tests are often used in conjunction with the HRNB, including the Wechsler Adult Intelligence Scale (various versions), measures of recent memory, further measures of sensory–motor integrity, and personality functioning (e.g., Minnesota Multiphasic Personality Inventory–2). Practices do vary from those who continue to employ the full HRNB and those who may select certain of the HRNB tests for specific and "flexible" purposes.

Based on the Cattell-Horn-Carroll theory of cognitive abilities,[10] the *Woodcock-Johnson Test of Cognitive Abilities, Fourth Edition* (WJIV)[11] offers an array of tests that provide a comprehensive view of neurocognitive skills. Findings from the WJIV can be compared to achievement abilities (Woodcock-Johnson Tests of Achievement), thus offering a method for evaluating learning disabilities or acquired disability relevant for academic planning. Clusters of neurocognitive abilities are assessed, including intellectual, comprehension–knowledge, fluid reasoning, short-term memory, cognitive processing and perceptual speed, auditory processing, auditory memory span, long-term retrieval, number facility, and cognitive efficiency.

One of the newer neuropsychological test batteries to be published that allows for both a fixed-battery and flexible-battery approach (i.e., the battery can be tailored to the needs of the clinical situation and patient) is the *Neuropsychological Assessment Battery* (NAB).[12] The NAB consists of a screening battery that allows for an overview of specific cognitive domains, and many clinicians will employ the screening battery to determine specific modules to administer, thus eliminating the need to administer all modules. The full NAB battery could be administered at the discretion and preference of the clinician as well. A particular benefit of this battery is that embedded in each of the neurocognitive modules (Attention, Language, Memory, Spatial, Executive) are tasks that purportedly have ecological validity. In the Attention module, a sequence of changing scenes behind the wheel of a car requires the examinee to identify items that are changed, new, or missing. In the Spatial module, there is a subtest that requires map reading and analysis. In the Memory module appear tasks requiring the recall of medication instructions, and name–address–phone number information appears. For the Language module, a task of bill paying and check writing appears. A set of questions pertaining to judgment and safety awareness is a part of the Executive module.

A popular shorter neuropsychological battery is the *Repeatable Battery for the Assessment of Neuropsychological Status* (RBANS Update),[13] which has four forms of the test—now with downward extension to the age of 12—and is applicable to those up to age of 89. There is a Spanish form of this test battery. The RBANS covers Immediate Memory, Visuospatial/Constructional, Language, Attention, and Delayed Memory. Many clinicians will also augment the RBANS with measure of executive abilities and sensory–motor functions that are not explicitly covered in the examination. For older adults, the *Kaplan-Baycrest Neurocognitive Assessment*[14] provides an option of a neuropsychological test battery that is standardized for this population.

FLEXIBLE-BATTERY APPROACHES

In flexible-battery approaches, the neuropsychologist may employ a different set of tests, depending upon the referral question and the type of neurological problem being analyzed. A combination of both qualitative and quantitative

methodologies may be used, depending upon the clinical situation at hand. The *hypothesis-testing approach* that has been championed by Muriel Lezak[15] is based on the idea that the presentation of the patient and the referral question generate initial hypotheses regarding the neurocognitive condition of the patient. Tests are selected to test out these clinical hypotheses. Confirmation and rejection of specific hypotheses can then lead to further neuropsychological testing to follow up clinical observation of test performance by the patient. Tests such as the Wechsler Adult Intelligence Scale, Rey-Osterrieth Complex Figure Test, California Verbal Learning Test, Trail Making Test, Wisconsin Card Sorting Test, and others are employed particularly in TBI due to the nature of commonly found impairments in this population. Although employing many standardized tests that those from other orientations administer, the hypothesis-testing approach is characterized by sequential steps in reasoning and an iterative clinical decision-making methodology when conducting the neuropsychological evaluation. Lezak et al.[15] describe this process as follows:

> Hypotheses can be tested in one or more several ways: by bringing in the appropriate tests…by testing the limits, and by seeking more information about the patient's history or current functioning… [it] may also involve changes in the examination plan, in the pace at which the examination is conducted, and in the techniques used…This flexible approach enables the examiner to generate multistage, serial hypotheses for identifying subtle or discrete dysfunctions or to make fine diagnostic or etiologic discriminations (p. 130).[15]

Another method by which neuropsychologists may evaluate the person with TBI is to opt for a more purely systematic qualitative approach. For example, the clinical methodology espoused by A. R. Luria[16] is characterized by a qualitative analysis of the patient's performance on a series of tasks, completed in a systematic manner.[17] Anne-Lise Christensen organized a set of Luria's behavioral neurology-oriented procedures into a systematic set of tasks called *Luria's Neuropsychological Investigation* (LNI).[18] The approach involves a set of procedures, including the preliminary conversation (stage one), which is the clinical interview. The next step involves the examination of motor, auditory, kinesthetic, and visual analyzers (stage two), followed by examination of specific cognitive functions (stage three) based upon performance of earlier stages of the examination. In the fourth stage of the examination (syndrome analysis), the clinician identifies the neuropsychological syndrome according to Luria's localization of functional systems in the brain. The LNI has been used for the purposes of brain injury rehabilitation and has been used specifically to evaluate those with TBI.[19] Although less known as a process-orientation type of neuropsychological instrument and thought of as a fixed-battery test, the Luria-Nebraska Neuropsychological Battery (LNNB) has, from its inception, involved a qualitative and process approach via the item analysis interpretation and syndrome analysis.[20] The rich clinical item content derives from Luria's original examination procedures, and, thus, the LNNB item content continues to lend itself to qualitative analysis and can serve to augment a number of approaches to neuropsychological assessment.

Another popular approach to the neuropsychological examination of patients with neurological disorders has been led by the late Edith Kaplan, called the *Boston Process Approach*. It often combines the use of fixed neuropsychological tests within a framework of examining not only the score outcome, and also the types and processes of the errors involved.[21] Kaplan and her colleagues originally utilize standardized tests (such as earlier versions of the Wechsler Memory Scale and the WAIS-R) and modified the administration procedures to introduce methods of scoring the protocol to analyze errors and to test the limits of the patient's cognitive capacity. Additional items and multiple-choice formats are added to the instrument to better analyze the performance of the patient. The WAIS-R-NI was a good example of that approach[20] in which the patient's constructions of the Block Design test are tracked, and certain kinds of errors (e.g., constructing the block patterns outside of the gestalt of the square) may be more indicative of right hemispheric impairment. Another example of the application of the Boston Process Approach is the use of the Rey Complex Figure test. Many neuropsychologists examine the quality of the copy portion of the test (i.e., examination of the reproduction of the patient's drawing of a complex geometric figure) for such pathognomonic signs as rotation, distortion of the figure, poor planning in the visuoconstruction aspects of the design, loss of detail, and problems in aligning angles and intersections of the design. Many examiners will assist in their analysis of the reproduced design by handing the examinee a different colored pencil at specific time intervals or after completion of specific elements of the design in order to better recount examinee's construction, allowing for a qualitative analysis of the drawing. The Boston Qualitative Scoring System for the Rey-Osterrieth Complex Figure was devised to quantify several elements and error categories of a patient's design reproductions.[23]

Although many neuropsychologists may not self-identify as utilizing a hypothesis-testing approach or use testing materials of the original Boston Process approach, most will continue to examine the qualitative aspects of test results in a manner that enhances the overall neuropsychological case conceptualization. Hence, there is less a demarcation between fixed and flexible approaches to neuropsychological evaluations. There is likely more convergence of testing procedures than there are specific and isolated "camps" of neuropsychological orientations.

CONTENT OF THE NEUROPSYCHOLOGICAL EVALUATION

In reviewing several neuropsychological evaluation procedures, it is important to both describe the instrument and

the cognitive domain that it represents. Describing the ecological validity implications is paramount so as to make the neuropsychological results relevant for the purposes of neurorehabilitation. As mentioned earlier in this chapter, ecological validity refers to a test's ability to predict everyday functioning. Sbordone[24] describes this concept as follows:

> Ecological validity can be defined as the functional and predictive relationship between the patient's performance on a set of neuropsychological tests and the patient's behavior in a variety of real-world settings (e.g., at home, work, school, community). This definition also assumes that demand characteristics within these various settings are idiosyncratic and fluctuate as a result of their specific nature, purpose, and goals. (p. 16)

The primary purpose of the neuropsychological evaluation is not often that of localization of lesions in TBI rehabilitation, but rather to describe a profile of neurocognitive assets and deficits that can be used in rehabilitation programming. They are useful when attempting to predict the patient's functioning in the environment and to assist with predicting the patient's behavior in "idiosyncratic" settings that do not remain static. According to Sbordone,[25] neuropsychological tests by themselves do not well predict everyday behaviors or vocational functioning. It is therefore incumbent upon the neuropsychologist to translate assessment findings into meaningful statements about a particular patient with specific deficits and under specific environmental conditions (e.g., inpatient rehabilitation unit setting, safety issues in being home alone without supervision, a job setting with noise distractions, college chemistry classroom setting). Ecological implications of particular testing procedures are stated for the following testing procedures.

It should be noted that issues of performance validity, symptom validity, and effort measurement in neuropsychological evaluations are not included in the ensuing discussion. Much has been written in this realm both in terms of research and clinical recommendations. The interested reader is referred to comprehensive texts, such as Boone[26] and Larrabee,[27] for in-depth treatment of this area. It also should be stated that common to neuropsychological practice is the administration of performance validity tests and examination of embedded measures of effort within the neuropsychological evaluation. Standardized tests, embedded indices, and behavioral observations of the patient are usually integrated to understand the veracity of obtained neuropsychological results.

Finally, the focus of the remainder of the chapter is on the adult neuropsychological evaluation of the person with TBI. Tables that appear in the remainder of the chapter are examples of tests that are often administered in the particular neuropsychological domain listed. This is not an exhaustive list as there are many others that are given routinely that do not appear here. The particular set of measures administered is unique to the neuropsychologist who is conducting the evaluation.

Cognitive screening and mental status examinations

Instruments that provide global information about general cognitive functioning can be useful in the assessment of patients with TBI to provide a brief look at level of ability. This tends to occur in the early phases of recovery when the patient may not be capable of engaging in a more complex or comprehensive examination. Table 31.2 provides a listing of common cognitive screening measures and their characteristics. These measures provide some coverage of important cognitive domains, such as recent memory, attention, visuospatial analysis and visuoconstruction skills, and abstracting and executive functioning skill (e.g., Cognistat, RBANS, Scales of Cognitive Ability for Traumatic Brain Injury). Others provide a global index of cognitive functioning (Mini-Mental State Examination, Clock Drawing Test). Although not used for diagnostic purposes, these tests are helpful when trying to determine whether or not a more comprehensive battery of neuropsychological tests may be recommended. Many of these tests are performed by other than neuropsychologists, including speech pathologists, occupational therapists, psychiatrists, physical medicine and rehabilitation physicians, and neurologists.

ECOLOGICAL IMPLICATIONS

These measures can assist rehabilitation team members answer such questions as the following:

- Does the patient have the mental capacity to understand his or her own cognitive condition?
- To what extent is the patient oriented and in need of supervision?
- Can the patient be expected to follow a schedule or keep up with simple instructions?
- What is the gross capacity of the patient to learn routines and carry over instruction from one time or setting to another?
- What is the global attention ability of the patient?
- Is there evidence for cognitive impairment that requires more in-depth neuropsychological evaluation to better define?
- Is there any relative preservation of cognitive ability that can be capitalized upon for simple tasks?

If the patient fails aspects of these cognitive screening measures, the rehabilitation team may need to provide interventions, such as the posting of a calendar in the patient's room for orientation purposes, cue the patient to the tasks at hand and encourage learning by repetition, determine the length of a session based on level of sustained attention, and train the patient to the setting and not assume transfer of learning to a new setting. Some measures, such as the

Table 31.2 Tests of cognitive screening and mental status examinations

Test	Comment
Screening Module of the Neuropsychological Assessment Battery (NAB)	Contains sections that correspond to the main cognitive modules of the full NAB: attention, language, spatial, memory, and executive functions. Provides recommendations for administering the cognitive module for clinical clarification if not giving the full NAB.
Cognistat (Neurobehavioral Cognitive Status Examination)	Assesses five major areas: language, constructional ability, memory, calculation skills, and reasoning/judgment.
Mini-Mental State Examination (Folstein)/Mini-Mental State Examination–2	Standard measure of mental state based on the 30-point scale; widely used for gross dementia detection; runs the risk of a high false negative rate. MMSE-2 includes a brief story recall and a coding task; can be scored for brief, short, and extended versions.
Montreal Cognitive Assessment (MoCA)	Brief measure of multiple cognitive domains, including a trail-making test, cube copy, clock drawing, list learning, attention items, sentence repetition, fluency, verbal abstraction, and orientation items.
Repeatable Battery for the Assessment of Neuropsychological Status Update	Brief measure of immediate memory, language, visuospatial/constructional, attention, and delayed memory; alternate forms are available for repeat testing. Not considered a classical screening battery, but subtests can be used for specific screening purposes.
Frontal Assessment Battery (FAB)	Brief bedside measure of common frontal system functions; includes items for abstracting, verbal fluency, motor programming, inhibition, and environmental control.
Scales of Cognitive Ability for Traumatic Brain Injury (SCATBI)	Measures cognitive and linguistic abilities and deficits; specifically tailored to those with TBI. The five subtests are Perception/Discrimination, Orientation, Organization, Recall, and Reasoning.
Shipley–2 (formerly the Shipley Institute of Living Scale)	Measures components of cognitive ability: crystallized knowledge (that acquired through experience and education) and fluid reasoning (learned through logic, problem solving, ability to learn new information). Vocabulary test measures crystallized knowledge; fluid reasoning assessed through sequence completion tasks and analysis of block patterns (Kohs cube designs); calculates an Impairment Index for adults. The Impairment Index is based on the discrepancy between vocabulary and abstracting scores.

RBANS and the NAB Screening Module, allow for repeat administration with which tracking cognitive improvements can occur. This may be particularly important when making discharge plans and organizing postacute neurorehabilitation services. The usefulness of RBANS is also underscored by its strength in distinguishing cognitive problems in those with TBI compared to noninjured controls, and moderate-to-strong specificity has been found to detect those with TBI.[28]

Cognitive screening measures may also be helpful in tracking the TBI patient's cognition in determining transfers to and from subacute and acute rehabilitation settings. The patient's ability to engage in 3 hours per day of rehabilitative therapy may depend upon the cortical arousal level and integrity of sufficient sustained attention and orientation to benefit from this intensive level of therapy. In special situations, such as the patient with combined spinal cord injury and TBI, making initial judgments about cognition may determine length of stay. In this clinical situation, decreased learning capacity and memory may result in the patient requiring more supervision, cues, and reminders and repetitive learning of such activities as executing proper transfers, self-catheterization, and repositioning to avoid decubitus ulcers.

Global level of performance

> Perhaps someone with expert knowledge of the human brain will understand my illness, discover what a brain injury does to a man's mind, memory, and body, appreciate my effort, and help me avoid some of the problems I have in life (p. xxi).[29]
>
> **L. Zasetsky in A. R. Luria's *The Man With a Shattered World***

A. R. Luria's method of behavioral neurology often involved the detailed examination of the patient[29] as documented in the cited work. His observations of the patient illustrate well an understanding of brain–behavior relationships after TBI. Luria's patient, Lieutenant Zasetsky, suffered a penetrating head injury from a bullet wound during World War II. Well described by Kaczmarek, Code, and Wallesch,[30] Zasetsky

was shot in March 1943, leaving him with significant deficits of memory, language, writing capacity, and executive functioning. Luria tracked this soldier's recovery and struggles over the course of greater than 25 years, chronicling by biography and Zasetsky's own writings the aftereffects of a severe brain injury. Aspects of generalized cognitive impairment and specific realms of cognitive deficits are highlighted by Zasetsky's case history and are referred to throughout the remainder of this chapter.

Based upon a larger set of neuropsychological test findings, indices of general neuropsychological performance and impairment serve similar functions as cognitive screening measures. They tend to have greater reliability because they are based upon scale scores summed across several domains rather than item-level scores. As mentioned earlier, the Halstead Impairment Index and Neuropsychological Deficit Scale of the HRNB are commonly cited general performance indices that have been used in TBI outcome research. The NAB can produce global indices for Attention, Language, Memory, Visuospatial, and Executive Functioning should all subtests be administered within each module. One limitation of the use of global impairment scores is that they are unable to describe in detail the specific cognitive problems that can explain problems in everyday functioning in the person with TBI. Table 31.3 presents measures of general neuropsychological level of performance.

ECOLOGICAL IMPLICATIONS

An index of general performance is an indication of overall neuropsychological integrity of higher cortical functions and can be used as a global proxy of a patient's ability to function independently in global life functions. Caution must be used in employing a global index alone, however, because it is more important to understand the specifics of neuropsychological assets and deficits that play a role in everyday activities. A global score alone cannot itself

Table 31.3 Measures of general levels of performance

Measure	Comment
Halstead Impairment Index	Calculation of the seven indexed tests of the HRNB; ranges from 0.0 to 1.0 with latter meaning seven out of seven of the tests fall in the impaired range.
General Neuropsychological Deficit Scale	Calculated off of 42 variables from the adult HRNB and allied procedures; higher scores indicate more impairment; each of the 42 scores falls in four score ranges (0 = perfectly normal; 1 = normal to mild impairment; 2 = mildly to moderately impaired; 3 = severely impaired performance); total GNDS scores fall into the following ranges: 0–25 (normal), 26–40 (mild impairment), 41–67 (moderate impairment), 68 and higher (severe impairment); total maximum score is 168 on the GNDS.
Luria-Nebraska Neuropsychological Battery–Form 1–Impairment Indices	The LNNB Impairment Index is calculated by examining the difference between the obtained T-score and the Critical Level; similar in concept to the NDS. In addition, there are other general measures of performance embedded within the LNNB: Pathognomonic, Left Hemisphere, Right Hemisphere, Profile Elevation, Impairment, and the Power/Speed calculation. The LNNB is in lesser use today, and no updated norms are available. Item analysis still possible to augment standardized neuropsychological measures.
Repeatable Battery for the Assessment of Neuropsychological Status Update (RBANS Update)	A total index score can be derived from administration of all subtests.
Wechsler Adult Intelligence Scale–Fourth Edition (WAIS-IV)	FSIQ not generally considered a neuropsychological measure; helpful in estimating long-term cognitive abilities; General Ability Index reflects robust and crystallized abilities for comparison to fluid abilities.
Wechsler Abbreviated Scale of Intelligence–Second Edition (WASI-2)	Four equivalent subtests derived from the WAIS-IV. A FSIQ can be derived from either use of all four subtests or two subtests. Subtests are Vocabulary, Similarities, Block Design, Matrix Reasoning.
Reynolds Intellectual Assessment Scales/Reynolds Intellectual Screening Test	Measures verbal and nonverbal intelligence in four subtests; shorter administration time than the WAIS-IV. Includes a measure of verbal and nonverbal memory. A screening version requires two-subtest administration.
Kaplan Baycrest Neurocognitive Assessment	Evaluates a broad range of functioning, including attention/concentration, immediate memory, delayed memory, verbal fluency, spatial processing, and reasoning/conceptual shifting.
Test of Nonverbal Intelligence–Fourth Edition (TONI-4)	A language-free test (both in administration and examinee responses); abstract and figural stimuli are used to evaluate general intellectual ability.

predict the complexity of home and community functioning. Hence, it may only be useful as a "ballpark" measure of brain functioning. Should a high deficit global score be obtained, this may suggest the person's capacity to independently generalize learned skills to new settings may be limited. A global index that falls in a mildly impaired range may be associated with a greater potential for independent living with which compensatory strategy training, modifications to the home environment, and training the patient with organizational aids may be feasible and effective. However, only by knowing these specific neurocognitive assets and deficits can the clinician determine which specific strategies will be useful in neurorehabilitation. Mild levels of global impairment do not necessarily connote mild impairments across all tests in a battery and could mean normal functioning on some tests combined with severe problems on specific tests. Compensating for the cognitive problem that falls in the severely impaired range (e.g., utilizing a memory aid for scheduling appointments and organizing information that impacts everyday functioning) may require the assistance of a rehabilitation therapist or family member to implement in everyday tasks or contexts. Depending on the time post-TBI, these general indices of impairment may take on different significance. A highly impaired global index at 1 month postinjury, improving to a mild level of global impairment within 3 months in a person with a moderate-to-severe TBI bodes well for longer-term prognosis. Contrasting this effect with a highly impaired global index at 5 years postinjury may suggest that further spontaneous recovery, to a larger extent, is highly unlikely given the persistence of significant and global cognitive impairment in that individual. Fluctuations in impairment indices across time may be reflective of situation specific or changes in non-neurological conditions (e.g., marked sleep disorders and coexistence of significant psychiatric or substance use issues).

Sensory–motor integrity

> When the doctor learned what my first name was, he'd always address me that way and try to shake hands when he came over. But I couldn't manage to clasp his hand… Suddenly, I'd remember and try to shake hands again but would only manage to touch his fingers (p. 46).[29]
>
> **L. Zasetsky**

Output of motor movement for everyday routine actions (e.g., picking up a jar, using the steering wheel while driving, carrying out mechanical tasks) may appear to be a reflexive action without involving higher cortical actions. Execution of motor programs cannot occur without the recursive feedback of tactile and sensory–perceptual inputs. The regulation of these sensory–motor circuits requires complex sequences of higher level cognition, especially when learning new motor actions. For example, motor programming, and inhibition of motor responses in favor of novel responding, requires significant frontal–subcortical integration. Luria posited that verbal mediation is a significant driver of human actions—what he described as the regulatory function of speech. Thus, the integration of higher cortical functions with motor movements and the ability to interpret tactile inputs is intricate. The interplay of motor functions and higher order processes occur and are relevant for consideration in brain injury rehabilitation. At another level, fine motor dexterity and speed (such as is required on the Grooved Pegboard Test) functions may specifically relate to general speed of cognitive processing, ability to use tactile sensation for adjusting motor programs, and persistence of motor behaviors. Table 31.4 describes commonly used tests of motor functions.

ECOLOGICAL IMPLICATIONS

Whether motor input impairment occurs in the peripheral nervous system (e.g., peripheral neuropathy), in the spinal cord (e.g., nerve dissection), at the subcortical level (e.g., cerebellar contusion), or at the cortical level (e.g., subdural hematoma damaging regions of the motor or sensory cortex and association areas), impairment in higher level abilities can be affected. Reduced motor input due to tactile sensory discrimination problems interferes with judgment of distance in low-light settings, for example. Centrally mediated problems, such as dysmetria or proprioception, may be compounded by impairments in sensory motor inputs. Training patients to scan and sweep their tactile environment may be less successful when sensory motor input of the fingers or hands is impaired. Reduced tactile discrimination and motor dexterity may prove disruptive to those patients who work on assembly lines, electrician work, musicians that utilize fine motor movement (e.g., violinists), and other professions that require fine motor dexterity. For example, organization of the motor act can be measured by Item 21 of the Luria-Nebraska Neuropsychological Battery (LNNB) and requires the patient to clench–extend the fingers alternatively between both hands (impairments on such motor acts is referred to as dysdiadochokinesia). Cognitive functions that are brought to bear on this item include fine motor speed, alteration and switching of motor acts (thus, requiring organization and rapid sequencing), and the ability to translate visual representation and verbally mediated instructions into accurate motor actions. Impairment on this item has implications for learning by visual demonstration, difficulty keeping and maintaining a sequence, and difficulty in maintaining motor coordination. All of these may be required to keep up with the instructions of the physical therapist to learn the proper way to range the arm or may implicate problems in coordinating syncopated movements in gait training (i.e., proper equal weight bearing on both feet, swinging the arms alternatively to maintain balance during gait). Changes in tactile–spatial

Table 31.4 Tests of sensory–motor functioning

Test	Comment
Motor Scale–LNNB	Multifactorial scale that examines simple motor output abilities to motor programs that require tertiary zone abilities; used clinically and in research contexts as a stand-alone measure.
Tactile Functions Scale–LNNB	Assesses a wide range of tactile input abilities, including tactile–spatial analysis, two-point discrimination.
Reitan-Klove Sensory Perceptual Examination	Given as a part of the HRNB to assess sensory–motor integrity; includes tests of tactile, auditory, and visual modalities.
Finger Oscillation Test	Part of the HRNB; motor speed and lateralization hypotheses can be assessed.
Hand Dynamometer–Grip Strength	Motor output strength and lateralization of deficits can be assessed.
Grooved Pegboard, Purdue Pegboard Test	Motor dexterity and speed is assessed; lateralization can be assessed.
Benton Finger Localization	Localization of fingers—conditions include hands visible and hands hidden from view.
Benton Motor Impersistence	Maintenance of movement and posture is assessed.
Benton Tactile Form Perception	Assesses spatial analysis and tactile recognition; assesses stereognosis.
Tactual Performance Test	Part of the HRNB; although multifaceted in nature, the TPT requires significant tactile–spatial analysis. This test is particularly helpful when testing those with vision impairments with whom visuoconstruction memory tests cannot be administered. Tactile–spatial problem-solving functions are also assessed by this test.

discrimination (Items 70 and 71 of the LNNB measure 2-point discrimination distance; aspects of the Reitan-Klove Sensory Perceptual Examination, such as Finger-Tip Number Writing) can impair the patient's ability to employ fine motor dexterity for such tasks as accurately executing keyboarding on the computer or precisely using applications on a smartphone and for a person with low vision and decreased ability to discriminate Braille symbols. Deficits in this realm can affect the mechanic who needs tactile senses to reach and manipulate parts on an engine carburetor that is not visible. Deficits of motor integrity can affect writing output ability and the ability to manipulate and utilize tools and could affect a person's ability for recreational and leisure pursuits, such as doing needlepoint or playing golf as well.

One patient with TBI that this author evaluated was a liver transplant physician who evidenced problems on the Tactile Functions scale of the LNNB with emphasis upon problems in his left (nondominant) hand. The patient described the need to use his left hand to reach underneath the liver while using his right hand to manipulate surgical instruments. The tactile senses of the left hand were required to identify structures of the liver and provide kinesthetic input regarding the position of the liver during transplantation procedures and thus required judgments that had to be made on a moment-to-moment basis during surgery. With impairments of these functions, the patient could no longer take the lead in doing transplant surgery. This illustrates one example of the critical nature of sensory–motor integrity to higher order abilities in a functional task.

Language functioning and pragmatics of communication

> By this time, I could remember a great many letters by associating them with different words, but when I tried to visualize a particular letter—"k," for example—or hunt up a word for it, I needed quite a bit of time in order to recognize it and point it out to my teacher (p. 68).[29]
>
> **L. Zasetsky**

The intricate relationship between higher mental processes and spoken language, according to Vocate,[31] was central to Luria's view of cognition:

> He [Luria] argues that "mind" is impossible without its synergetic relationship with spoken language and that both arise from the physical reality of the human brain and human society. (p. 129)

She goes on to summarize Luria's thought by stating that "spoken language is the means by which the individual becomes capable of conscious and voluntary processes" (p. 143) and that language "is a component in the complex functional systems of other higher mental processes" (p. 146). Indeed, language acquisition is a lynchpin to the acquisition of knowledge and engagement in the sociocultural environment. When there is dysfunction of language ability after TBI, there usually exists significant disruption in the patient's ability to interact with the social

environment (e.g., family members, coworkers, friends). Language dysfunction also has implications for other cognitive processes that rely on receptive language functions, such as recent verbal memory ability. In the Western world where there is heavy reliance on language abilities, deficits in language and communication skills can be disabling. Another aspect of language includes the pragmatics of communication. These may include such variables as excessive verbal output, paucity of verbal output, tangential prose, and circuitous narrative verbalizations. Verbal interruptions and decreased ability for conversation turn exchange can also be a part of pragmatic communication. Although the latter pragmatics issue may be best assessed by observation, language-based neuropsychological tests can be useful in providing tasks that elicit problems with communication pragmatics. Table 31.5 describes common neuropsychological tests that evaluate language functioning in the patient with TBI. The larger language batteries (e.g., Multilingual Aphasia Examination, Boston Diagnostic Aphasia Examination, Western Aphasia Battery) are each able to classify aphasia syndromes: global, mixed transcortical, Broca's, transcortical motor, Wernicke's, transcortical sensory, conduction, and anomic aphasias. Key variables that are assessed to ascertain these subtypes include tasks of spontaneous speech, fluency, naming, comprehension (auditory and nonverbal), repetition, reading, and writing. It should be noted that speech pathologists are expert in language assessment, and there is considerable overlap between measures used by speech pathologists and those employed by neuropsychologists. Speech pathology evaluations may reveal the impact of motor speech (speech apraxia, dysarthria) impairments on the production of language in order to distinguish these deficits from that produced by impairments in higher cortical functions.

ECOLOGICAL IMPLICATIONS

Language impairment after TBI can come in many forms, including different forms of aphasia, impairments of oral word fluency, and disorders of pragmatic communication skills. Expressive language disturbances influence everyday activities, such as use of the telephone. If a patient cannot properly communicate safety conditions over the telephone, that patient's safety at home without continuous supervision is threatened. Paraphasias can disrupt interpersonal communications and can be experienced as markedly frustrating to the patient. A dynamic can quickly develop with well-meaning family members and friends who will assist the patient by filling in the correct word or speaking for the person with TBI. Those with global aphasia experience marked limitations in independent living ability due to the

Table 31.5 Tests of language functioning

Test	Comment
Woodcock-Johnson IV Tests of Achievement/Woodcock-Johnson IV Tests of Oral Language	A battery of tests of academic achievement; oral language subtests.
Multilingual Aphasia Examination–Third Edition	Focuses on oral expression, spelling, oral verbal comprehension, reading, and the assessment of articulation.
Boston Diagnostic Aphasia Examination–Third Edition	Comprehensive set of measures that correspond to a full range of aphasia types.
Boston Naming Test	Confrontation naming task that allows for semantic and phonemic cueing; can be used separately from the Boston Diagnostic Aphasia Examination.
Neuropsychological Assessment Battery (NAB) Language Module	Two forms includes subtests for auditory comprehension, reading comprehension, confrontational naming, writing, and a bill-paying task.
Token Test	Commonly used to evaluate the ability to follow commands of increasing complexity.
Controlled Oral Word Association Test	Measures word fluency; executive processing may influence performance on this test.
Neurosensory Center Comprehensive Examination for Aphasia	Consisting of 24 subtests, it also includes tests that evaluate visual and tactile function. These latter tests are given when a task requires visual or tactile functions that are impaired, thus allowing for discrimination of primary language from competing reasons for the presence of impairment.
Reitan-Indiana Aphasia Screening Examination	Part of the HRNB; tasks are easily passed by normal adults; identifies pathognomonic signs of aphasia; tends to be a gross screening measure of language requiring further detailed examination.
Western Aphasia Battery–Revised	Evaluates reading, writing, calculation ability, and nonverbal skills; yields an Aphasia Quotient, Cortical Quotient, Auditory Comprehension Quotient, Oral Expression Quotient, Reading Quotient, and Writing Quotient.

limits imposed by both receptive and expressive language abilities. Speech pathologists are adept at identifying, evaluating, and treating an array of aphasic disorders. In the context of rehabilitation, knowing the nature of communication problems that arose from the TBI can assist other therapists in their work with the patient. For example, those with receptive language impairments experience problems with following instructions presented by the therapist. They may require alternate modalities (visual presentation) or multiple modalities (presenting information by use of both visual and procedural–kinesthetic input) of instruction to accomplish a task. For example, a patient with both expressive and receptive language dysfunction may need to have the therapist demonstrate how to put on an ankle–foot orthosis and may also need the therapist to physically direct his or her hands and legs to learn the procedure and minimize the sole use of verbal instruction.

Working memory and complex attention processing

> I try a little harder to remember and make sense of the person's remarks. And when I talk to my mother or sisters, I have to strain my nerves and memory even more to understand what they're saying to me so that I know what I'm to do or say (p. 93).[29]
>
> **L. Zasetsky**

Working memory refers to that ability to register and manipulate information. Baddeley referred to this concept as the central executive system.[30] It requires the patient to hold initially encoded information while being able to manipulate that information and store the newly manipulated information for immediate future use. Working memory is invoked when executing mentally, for example, a four-digit subtraction task. Often, visual representation, auditory attention, retrieval of long-term information, and executive abilities can be employed in working memory tasks. Once information has been initially processed, information can then be encoded into recent memory storage.

Encoding of information requires the person to process that information at a rate commensurate with signal reception. For example, when a person is listening to a lecture in a classroom, the instructor may deliver information in multiple modalities (visual computer generated slides, talking to those slides, talking somewhat quickly and sometimes tangentially). The delivery of that information may affect the listener who is trying to attend to these multiple modalities, filter out information that is irrelevant to the task at hand, and process these multiple modalities at a rate of multitasking that allows for an adequate level of encoding and storage of that information. Being able to process such information requires all four aspects of cognitive processing as proposed by Luria and further explicated by J. P. Das, known as *PASS Theory*.[33] This theory conceptualizes brain–behavior functioning in terms of four dynamic processes that are brought to bear by a cognitive challenge: Planning, Arousal–attention, Simultaneous, and Successive processing components (PASS). Thus, complex attention processing involves multiple components of cognition that work in concert. The PASS model can be assessed through Neo-Lurian–based instruments, such as the Cognitive Assessment Scales (for children and adolescents), Kaufman Short Neuropsychological Assessment Procedure (K-SNAP), Kaufman Adolescent and Adult Intelligence Test (KAIT), and the Luria-Nebraska Neuropsychological Battery (LNNB). The model lends itself to much application in neurorehablitation[34] and can describe tasks that occur in everyday functioning.

Another aspect of complex attention processing includes the trade-off between processing speed and accuracy of processing. Accuracy can include the error rate that occurs during a cognitive task with a specific time limit or task completion constraint. Battistone, Woltz, and Clark[35] argue that some individuals with TBI may, in fact, have difficulties in allocating their cognitive resources to a challenging task. Some show problems with processing capacity, and others demonstrate volitional actions toward slowing processing. Both processes of processing capacity and invoked cautiousness may play a role in problems with effective encoding of information.

Conceptually, there is a close relationship between working memory and recent memory abilities. Individuals with TBI have difficulty in working memory that some believe is a result of dysfunction of the central executive system and related to higher order executive functioning deficits.[36] Some argue that patients with TBI do not, primarily, exhibit problems in working memory but in recent memory processes of encoding, consolidation, retention, and retrieval.[37] Some recent evidence by Sandry, DeLuca, and Chiaravalloti[38] also suggests that working memory ability after TBI mediates the relationship between cognitive reserve and long-term memory abilities. Further, their research is consistent with the prospect of working memory as a foundational mechanism of cognitive reserve.

Complex attention processing includes the ability to sustain and focus attention on a task. Alternating and divided attention also come under this category of cognition. The research literature clearly shows that attention deficits are common among those with TBI (e.g., Van Zomeren, Brouwer, and Deelman[39]). Impairments in attention appear to occur across the spectrum of TBI, including mild TBI, the latter showing impairments on tests of attention that requires information processing speed.[40] Table 31.6 presents some common measures of working memory and complex attention.

ECOLOGICAL IMPLICATIONS

Working memory and processing speed impairments can be significantly disabling due to the need for this aspect of cognition in most human activities. Although those without brain injury may be able to carry out routine everyday

Table 31.6 Working memory and complex attention processing measures

Test	Comment
Working Memory Index–WAIS-IV	Comprised of the Arithmetic, Digit Span, and Letter-Number Sequencing subtests.
Processing Speed Index–WAIS-IV	Comprised of the Digit Symbol–Coding and Symbol Search subtests; requires motor writing output.
NAB Attention Module	Includes orientation items, digit span, dot visual attention task, number/letter cancellation tasks, and a driving scene task.
Ruff 2 and 7 Selective Attention Test	Measures both accuracy and speed of selective attention; normative sample includes those with TBI.
Auditory Consonant Trigrams Test	Evaluates alternating and divided attention in the auditory modality; executive functioning also influences performance; has been referred to in the literature as the Brown-Peterson test.
Paced Auditory Serial Addition Test	Sustained attention test; significant demands on working memory; information processing speed is also assessed without the need for motor writing output; used frequently in TBI; there are several versions of this test that include different internumber timed intervals.
Continuous Performance Tests	Examines lapses in attention, vigilance, and impulsive responses; computerized administration.
d2 Test of Attention	Speed and accuracy of selective attention is measured; can be used with children and adults.
Brief Test of Attention	Assessment of auditory divided attention; broad normative base.
Visual Search and Attention Test	Visual letter and symbol cancellation task; examines ability to sustain visual attention.
Digit Vigilance Test	Produced for visual tracking and target selection of visual stimuli.
Stroop Color–Word Test	Attention, cognitive flexibility, and response inhibition are assessed; commonly used are the Golden and Trenerry versions. A similar version of this test appears in the Delis-Kaplan Executive Function System (D-KEFS) and is called the Color–Word Interference Test. The latter adds a switching component to the task, likely invoking executive abilities.
Test of Everyday Attention	Evaluates divided, alternating, selective, and sustained attention; approach uses everyday materials that may better approximate real-world situations.
Symbol Digit Modalities Test	Visual tracking, motor speed; comparisons between written and oral performances can be provided. Similar to the Coding Subtest of the WAIS-IV except numbers are coded instead of symbols.
Trail Making Tests, Parts A and B	Cognitive flexibility and speed of information processing are assessed; other similar versions include the Comprehensive Trail Making Test (CTMT) and, from the Delis-Kaplan Executive Function System, the Trail Making Test.
Color Trails Test	Similar concepts as Trail Making Test but uses colors instead of letters; can be given without verbal instruction; alternative research forms are available.

activities at a preconscious level, working memory impairments in those with TBI can be experienced as confusion, derailment, and poor task maintenance. Working memory impairments are evidenced early after TBI and may significantly contribute to posttraumatic amnesia. In acute rehabilitation, clinicians may be required to cue the patient to the task at hand and may need to direct the patient through the component steps of a task. In severe TBI, an occupational therapist may need to break down the morning ritual of brushing teeth and washing the face into much smaller parts. This type of incapacity can be puzzling to family members who may assume that the patient may have forgotten how to brush the teeth (i.e., long-term memory loss) when, in fact, that patient has difficulty registering information related to the context of teeth brushing and may have difficulty not only with simultaneously processing positioning the tooth brush appropriately while alternating the brushing motion and also in making the decision as to when to discontinue the task. Difficulties with alternating and divided attention can result in the patient being easily distracted from the task at hand. In an office environment, an office clerk with divided attention problems may not be able to focus attention on the telephone while, in the background, coworkers are moving about the room. This is akin to the cocktail party phenomena in which most without brain injury may be able to focus on one conversation while ignoring others,

then turn their attention to another speaker, again without being distracted by extraneous conversations. The patient with TBI may have difficulties shifting the focus of attention efficiently and will encode incomplete information and may incorporate information from extraneous conversations due to difficulties sifting out appropriate auditory stimuli. Referring to the PASS model, these situations may overtax the simultaneous and successive cognitive functions of the person with TBI with the net result that of poor encoding of relevant information and, later, poor retrieval of information. In everyday conversations, the rate of verbal delivery of information from a speaker may outdistance the rate of processing available to the person with TBI. Teaching family members and significant others ways of slowing down their pace of conversation, allowing for breaks and repetition when needed, can benefit the listener who may have trouble with simultaneous and successive processing of verbal information. Often, patients will describe being easily overstimulated and overwhelmed when there are too many noise or visual distractions in the immediate environment. Although many will describe this as "multitasking," the same PASS model demands are in play, and as a result of TBI, that individual may not be able to process information due to deficits in each of the four PASS components, leading to feeling anxious or frustrated in these multitasking situations. Reading tasks can be affected by impairments in visual sustained attention. Tracking words across the page with the aid of a ruler or use of a finger to cue eye movement can help compensate for a patient's difficulties with sustaining attention on the written text. Having the patient articulate the words aloud while they read may also assist with self-cueing and focusing attention on a reading task.

Speed of information processing

As noted earlier, several neuropsychological tests judge the accuracy and speed of information processing. Individuals without brain injury are usually capable of completing tasks both accurately and within a reasonable period of time. After TBI, one or both aspects of information processing may be impaired. The Wechsler Adult Intelligence Scale–Fourth Edition contains four indices that are analytically derived from the subtests of the test. The Verbal Comprehension, Perceptual Organization, and Working Memory Indexes require accurate responses, and the patient is penalized less for time of completion. An exception to this is the Block Design test in which the correct response is recorded, but more points are awarded with a more rapid correct response. The Processing Speed Index provides a measure of information processing efficiency. Speed of information processing for response inhibition, as measured by the Stroop Color–Word Test and motor output speed on the Purdue Pegboard, has been shown to be associated with general functional outcomes (operationalized by the Glasgow Outcome Scale) in patients with moderate-to-severe TBI.[41] The analysis of speed versus accuracy is also obtainable on tests such as the Ruff 2 and 7 Selective Attention test on which selective attention accuracy (errors of omission and commission) and amount of information processed (accurate target detection speed) are measured. The relative mix of accuracy and speed can be calculated from a subset of items from Form I of the LNNB termed the Power and Speed Indexes. As with most neuropsychological tests, there are few that purely measure a single construct. For example, the Delis-Kaplan Executive Function System Color–Word Interference Test measures information processing speed and response inhibition as well as shift set maintenance. There is considerable overlap between attention abilities and information processing speed. Table 31.6 includes measures of information processing speed.

ECOLOGICAL IMPLICATIONS

During the acute inpatient stay, the patient is often engaged in many rehabilitative therapies, each with different tasks and learning goals. The rate of learning these routines and benefiting from treatment may depend on the patient's capacity for information processing speed. It may be important, therefore, to pace the patient through a mobility or ambulation exercise in a way that does not exceed the patient's ability to keep up with instructions. Repetition of instruction and slowing down the rate of verbal output on the therapist's part can improve the patient's understanding of the task. In the postacute phase, therapists may elect to improve either accuracy or speed, depending upon the task to be mastered. Those patients with whom behavioral impulsivity and disinhibition may be problematic may benefit from an approach that focuses on pacing the speed of response and inserting verbal self-cueing methods between the instruction and execution of the task. In making job modifications, the patient with brain injury may require that tasks be done on a project-driven basis rather than a time-to-work product basis, thus with reduced demands for speed of processing perhaps with an emphasis on accuracy. It may not be possible for the patient to work full time and produce the amount of work prior to TBI, but working part time on a limited set of projects may better accommodate speed of information processing deficits. Resolving these processing speed problems may require a clear assessment of the patient's current capacities and slowly building his or her efficiency by working on accuracy (reduced rate of errors), then increasing speed while not increasing error rate.

Recent memory functioning

> I used to spend all my time lying on my right side or sitting up for a little while trying to recall some of my past. I couldn't remember anything at will, whereas, when I wasn't thinking about anything in particular, some words would occur to me along with the tunes of different songs. I'd hum to myself (p. 89).[29]
>
> **L. Zasetsky**

Recent memory is a multifaceted concept covering verbal, visual, and tactile–spatial domains. Memory can include episodic (event-related memory) and procedural (recall and reproduction of actions) aspects. Although the scope of this chapter does not allow for a thorough review of memory functioning in TBI, some highlights are in order to better describe ecological implications. For a comprehensive discussion of the neuropsychology of memory, see Squire and Schacter,[42] Tulving and Craik,[43] and Addis, Barense, and Duarte.[44]

A number of studies have examined memory dysfunction in TBI. A common measure of recent memory is the California Verbal Learning Test with which Wiegner and Donders[45] found attention span, learning efficiency, delayed recall, and inaccurate recall being components of memory disorder among patients with TBI. Patients with TBI have been found to have a rapid rate of forgetting new information and difficulties with the consolidation of new material.[46] Material-specific memory or that ability to recall information based on the properties of the stimulus material (verbal, visual–spatial) has been found to underlie episodic memory in TBI.[47] Capitalizing upon enhancing stimulus materials may, therefore, assist the learning process in this population.

Recent memory ability and new learning skills are intimately linked, seen in the neuropsychological evaluation of these skills and also observed in everyday situations. This is consistent with the literature that states that memory deficits in those with TBI can also be attributable to general cognitive deficits, particularly in those with moderate-to-severe TBI.[48] Frontal system deficits and the self-regulatory and self-monitoring aspects of the frontal–subcortical system may play a significant role in the registration, encoding, storage, and retrieval of information. Those with self-awareness deficits may not pay attention to information that could be judged to be important to recall at a later time. Those with disinhibition syndromes may not have the sustained attention necessary to register important information, and therefore, storage of such relevant information may be incomplete. Thus, memory functions are highly regionalized from a brain–behavior perspective, and evaluating key components to the process of storage and retrieval is a critical aspect of neuropsychological evaluations in those with TBI. Unlike focal strokes, those with TBI may demonstrate an array of regional brain dysfunction that can affect functional memory ability in a variety of ways. Thus, examination of attention processes, working memory mechanisms, information processing speed efficiency, and executive abilities is crucial to understanding the nature of memory deficits in those with TBI.

Another aspect of memory that is not easily ascertained is prospective memory capacity. Henry et al.[12] refer to this form of memory as "…memory for future intentions" (p. 457). This form of memory also requires executive abilities, including planning, anticipation, and self-monitoring functions. Although many tasks examine recent declarative or episodic memory functions, few are geared to determine prospective intent. Two available tests that measure this aspect of memory include the Cambridge Prospective Memory Test and the Rivermead Behavioural Memory Test—Third Edition, and these are noted in Table 31.7.

In clinical practice, recent memory tests assess immediate recall of information for which efficient encoding of information is required. Immediate recall paradigms include both verbal (e.g., word-list learning tasks on the CVLT-II) and visual (e.g., Immediate Recall of the Rey Complex Figure Test) components. Delayed recall of initially presented material across 20- to 30-minute time intervals are common among memory tests. The examiner will usually administer other neuropsychological tests/tasks in the interval time between the immediate and delayed recall portions of the test, thus introducing an element of alternating, focused, and divided attention. This can be helpful in evaluating the person with TBI in that delayed recall may be affected by distracting tasks or stimuli, thus interfering with retrieval of previously learned information. Tests such as the CVLT-II, Rey Complex Figure, and the Tactual Performance Test employ an incidental memory paradigm whereby the examinee is not prompted that recall of test stimuli or verbal information will be asked for at a later time. Other memory tests such as those that appear on the NAB Memory Module provide the prompt for later recall.

Recognition trials in which the patient must choose among several verbal or visual stimuli to identify what was initially presented assess recall accuracy, false positive, and false negative rates. Recall trials often require rote retrieval of information and are generally more difficult for the patient. Recognition trials allow for an assessment of storage capacity (i.e., if the patient accurately recognizes information, it is assumed to be stored). Verbal and visual stimuli may be placed within a context such as a paragraph story that has a beginning, middle, and ending; visual stimuli may be recognizable objects or pictures. Other recent memory tests may require the patient to impose an organizing principle (e.g., word-list learning tests, such as the Bushcke Selective Reminding Test or the Rey Auditory Verbal Learning Test) in order to recall stimuli. Still, others may cue the patient to categorize earlier presented information (e.g., on the California Verbal Learning Test, the examiner asks the patient for all of the tools and vegetables that are on the list). Table 31.7 presents some common memory tests that are utilized in the context of brain injury rehabilitation.

ECOLOGICAL IMPLICATIONS

Among the various types of cognitive problems presented by the patient with TBI, memory disorders may be more easily compensated for with the use of compensatory strategies (cf. executive functioning problems). Upon identifying the type of memory problem the patient presents, other functional systems may be employed to compensate. A traditional example is the patient with recent verbal memory deficits in delayed recall for whom a memory book and training on the routine use of the memory book can capture information that may be lost due to recall deficits.

Table 31.7 Tests of recent memory functioning

Test	Comment
Wechsler Memory Scale–III, Wechsler Memory Scale–IV	Normed with WAIS-III/WAIS-IV; WMS-IV includes expanded normative base for older adults; includes indices for Auditory Memory, Visual Memory, Visual Working Memory, Immediate Memory, Delayed Memory.
NAB Memory Module	Word-list learning, story memory, and shape-learning tasks along with tasks for daily living—medication instruction learning, name–address–phone number learning.
California Verbal Learning Test–Second Edition	Word-list learning test of verbal memory; many indices can be calculated, including the effect of interference, category cues, and recognition on memory performance; norming includes TBI; adult and children's versions are available; short-forms and alternate forms also available.
Rey Auditory Verbal Learning Test	Word-list learning test; several different norm tables are available; different word lists are also available.
Buschke Selective Reminding Test	Word-list learning test; widely used in research with TBI; executive functioning ability influences test performance.
Hopkins Verbal Learning Test–Revised	Word-list learning test with delayed recall and recognition tasks; multiple forms of the test are available.
Brief Visuospatial Memory Test–Revised	Design learning test with delayed recall and recognition tasks; multiple forms of the test are available.
Memory Assessment Scales	Measures recent verbal and visual memory across 12 subtests.
Tactual Performance Test	Part of the HRNB; measures incidental tactual memory; requires problem-solving, tactile–spatial analysis, and speed of information processing.
Rey Complex Figure and Recognition Trial	Measures visuospatial memory; provides a recognition trial; can measure visuoconstruction ability and planning ability; qualitative scoring systems are available for other versions of this test.
Rivermead Behavioural Memory Test–3	Evaluates everyday memory ability; includes elements of prospective memory; expanded normative groups; includes the Novel Task test that evaluates a person's ability for new skill learning.
Extended Complex Figure Test	Similar to the Rey Complex Figure test paradigm; adds recognition and matching tasks to differential visual–spatial memory recall and recognition from visuoconstruction difficulties. Includes matching and recognition scores for left and right fields of the complex figure; includes a short form.
Test of Memory and Learning–Second Edition	Core indices are verbal memory, nonverbal memory, and composite memory. Note: These three same indices by the test authors appear as a part of the Reynolds Intellectual Assessment Scale. Also contains supplementary indices: verbal delayed recall, learning, attention and concentration, sequential memory, free recall, and associate recall.

Employing an organization strategy, assuming relatively intact new learning and executive ability, allows for the patient to successfully utilize the memory aid. A patient with the same verbal memory deficit may be aided by training to visualize information to be recalled and to learn new information in multiple modalities including visual, tactile, and by verbal repetition.

Rehearsal of important information, paired with cueing techniques (e.g., a watch alarm, visual reminders such as a green dot placed in strategic places in the house or work setting), may also aid recall accuracy. Consistency of recall of information may require compensatory or environmental manipulations that assist with complex attention problems that may play into recall deficits. Reducing extraneous noise in the environment may allow the patient to better encode and store needed information. Improving lighting conditions during reading activities may also improve encoding of written material, thus improving storage efficiency. One of the difficulties in training the patient in compensatory memory techniques is the problem of "remembering to remember," otherwise known as *metacognition*. Supervisory attention and executive abilities must be intact, to a certain degree, in order for the patient with TBI to successfully utilize memory aides. With the proliferation of personal technology (e.g., smartphones and personal tablet computers with an array of applications available), there exists extensive opportunities in developing compensatory aides for those with neurocognitive impairments after TBI.

Visuospatial analysis and visuoconstruction ability

> Ever since I was wounded, I've had trouble sometimes sitting down in a chair or on a couch. I first

> look to see where the chair is, but when I try to sit down, I suddenly make a grab for the chair since I'm afraid I'll land on the floor. Sometimes that happens because the chair turns out to be further to one side than I thought (p. 47).[29]
>
> **L. Zasetsky**

> Not only would he "lose" the right side of his body (an injury to the parietal area of the left hemisphere inevitably produces this symptom), sometimes he thought parts of his body had changed—that his head had become inordinately large, his torso extremely small, and his legs displaced. It seemed to him that, in addition to the disintegration of objects he perceived, parts of his body had undergone some form of fragmentation (p. 42).[29]
>
> **A. R. Luria**

Impairments of visuospatial and visuoconstruction abilities can occur after TBI and may take on many different forms. The patient may evidence problems with visual–spatial analysis of visual percepts. On Block Design of the WAIS-IV, for example, the patient may not be able to construct visual designs using different patterned and colored blocks and may lose the whole or gestalt of the design. More esoteric problems in TBI may present as something like Gerstmann's Syndrome[49] in which the combination of *agraphia* (difficulties in motor writing with spelling and word order altered), *acalculia* (deficits in execution of arithmetic calculations), *finger agnosia* (inability to name or move a designated finger after it has been labeled), and *right–left confusion* (discrimination of instructions that require orientation of the right vs. left side of the body) occurs. Recognition of common objects could occur as a function of an acquired visual agnosia after TBI. Any or all of these components can be evidenced in TBI, likely due to the cortical proximity of brain regions that mediate these activities (emphasis on the left parietal region). Impairments of perceptual–motor integration refer to the general inability of the patient to properly visualize information, translate the visual percept into an accurate cognitive representation, and then execute an accurate motor response, such as copying a design that corresponds to the original percept. In *constructional dyspraxia*, the patient's written reproductions of designs may be distorted or rotated with loss of the spatial configuration of the original visual stimuli. Assembly of materials may be impaired due to visuoconstruction impairments. Table 31.8 shows some common tests in this domain.

ECOLOGICAL IMPLICATIONS

Mechanical abilities rely heavily on intact visuoconstruction skills. In the early phases of rehabilitation, activities of daily functioning can be affected by impairments of these skills. Dressing activities that require sequencing of steps and accurate right–left orientation skills may be impaired. Therapists will often face the patient when demonstrating a technique or skill, and this requires the patient to translate what is seen to actions, requiring accurate right–left orientation. Rather than facing the patient, it may be beneficial to work side-by-side to reduce the need for the patient to translate the visual orientation of the task. Later, in the postacute

Table 31.8 Visuospatial analysis and visuoconstruction ability tests

Test	Comment
Perceptual Reasoning Index–WAIS-IV	Composed of core subtests of Block Design, Matrix Reasoning, and Visual Puzzles; supplemental subtests are Picture Completion and Figure Weights.
NAB Spatial Module	Visual discrimination, design construction, figure copy, and map-reading tasks.
Rey-Osterrieth Complex Figure Test	Design reproductions can indicate impairments of perceptual–motor integration.
Benton Judgment of Line Orientation	Measures visuospatial judgment.
Benton Visual Form Discrimination	Measures visual accuracy and discrimination ability.
Benton Facial Recognition	Ability to match unfamiliar faces is tested; can assess prosopognosia.
Benton Right–Left Orientation	Measures the ability of the patient to accurately identify body parts on the appropriate side of the body.
Hooper Visual Organization	Allows for the measurement of visuospatial integration without a motor response.
Line Bisection Test	Measures problems with visual neglect, precision of spatial alignment.
Visual Object and Space Perception Battery	Eight subtests measure spatial perception, spatial estimation, and spatial localization.
Visual Functions Scale–LNNB	Items measure visuospatial, visuoconstruction, and visual judgment abilities; executive functioning abilities are required for some of these items.

phase, community mobility, driving ability, and detailed activities, such as filling out a job application or organizing the kitchen, may be affected by visuoconstruction impairments. Pathfinding skills may need to be aided by verbal instruction, enhanced visual cues, and rehearsal of the task to encourage procedural learning. The person with TBI may have trouble navigating, judging distances, and negotiating the living environment or have trouble with mobility in the community due to visuospatial deficits. Reading ability may also be affected, and dyslexia (impairments in reading) may have a component of dysgraphia; in combination, they reduce reading efficiency. Large-print materials and cueing techniques may be helpful in these situations. Alternate learning systems, such as audiobooks and use of speech recognition software for written material, may be of assistance.

Executive functioning

> I can't understand how wood is manufactured, what it is made of. Everything—no matter what I touch—has become mysterious and unknown. I can't put anything together myself, figure anything out, or make anything new. I've become a completely different person, precisely the reverse of what I was before this terrible injury (pp. 98–99).[29]
>
> **L. Zasetsky**

The term *executive* in executive functioning ability is a term apropos to the construct being measured. It refers to the capacity to encode and utilize information from a variety of sources, process that information quickly and efficiently, and then, engage in decision-making based on those inputs—much like what a business executive engages in on a daily basis. Executive processes are most often associated with frontal lobe functioning and a multitude of research has been conducted to examine the executive abilities associated with this brain region (see Miller and Cummings[50] and Stuss and Knight[51] for a comprehensive examination of frontal lobe functioning). Luria[5] described executive abilities as residing within the tertiary zone of the brain, and this is the unit responsible for the "programming, regulation, and verification of [mental] activity" (p. 79). What Luria[52] also understood was the interconnections of the tertiary zones with other zones in the brain, and he delineates a neuropsychology of problem-solving not only involving the frontal lobes, but also implicating parietal–occipital and basal–frontal functional systems.

A significant amount of research has been devoted to understanding the nature of executive functioning impairments in TBI and the extent to which such deficits are remediable. Executive functioning deficits, measured by the Wisconsin Card Sorting Test and the Tower of Hanoi/London test, are related to acute neurophysiological damage in TBI survivors.[53] A study by Greve et al.[54] demonstrated that patients with TBI can be clustered into four different executive functioning groups: 1) intact performance, 2) impaired response maintenance, 3) problem-solving impairment, and 4) impairments in ability to shift cognitive set. Executive functioning ability may also overlap with neurobehavioral impairments, such as emotional dyscontrol and reduced motivation.[55]

Common to the evaluation of executive abilities are tasks of set shifting ability, efficiency of verbal fluency, response inhibition, planning and organization skill ability, abstract reasoning ability, and categorization of concepts into higher-order sets. Ability for judgment and social reasoning can be included as a part of executive functioning.

According to a well-known model of frontal systems by Stuss and Benson,[56] self-awareness is the highest human cognitive capacity that is served by a number of other executive abilities. Abilities such as anticipation, goal selection, preplanning, drive, sequencing, and self-monitoring all contribute to self-awareness ability. Self-awareness deficit, also known as *anosognosia*, is a perplexing problem in those with TBI, and rehabilitation of these deficits is a challenging endeavor.[57]

The Stuss-Benson model is consistent with Lurian theory with the tertiary zone comprising the first three tiers of the model, and the fourth tier is related to Luria's secondary zone. These aspects of executive functioning are well represented in many of the tests employed by neuropsychologists (see Table 31.9).

ECOLOGICAL IMPLICATIONS

A problem noted by Cripe[58] in connection with testing for executive abilities is the ability to generalize test findings to real-world settings. In the clinical setting, testing occurs in a controlled environment with a minimization of distractions, usually administered by an examiner who can cue and encourage the patient's behavior. This is in contrast to real-world settings that are less structured and require the patient to impose structure and organization to function, require planning and self-initiation on the part of the patient, and in which the environment may be competitive in nature in the absence of a test examiner who can encourage and redirect the behavior of the patient. Neuropsychology laboratory tests may not best represent what the patient can and cannot do in the real-world environment.

Nevertheless, tests of executive functioning can be predictive of outcome. A study by Sherer et al.[59] found that the Trail Making Test (Part B) is particularly effective in predicting productive outcomes in patients with TBI. This is thought to be true due to this test requiring dual-task performance (simultaneous processing) and speed of information processing. Although not specifically cited as tests of executive functioning, tests such as the Trail Making Test or Color Trails Test require cognitive flexibility, dual-task performance, alternating attention, working memory, and speed of processing, all working together in concert. This harkens back to what Luria described as the regulation and verification of higher mental processes. These represent complex and high-level cognitive skills and are not easily

Table 31.9 Tests of executive functioning

Test	Comment
Delis-Kaplan Executive Function System	Battery of executive functioning tests, many that parallel existing and commonly used executive function tests; advantage of subtests that are standardized together to compare scores across executive functioning domains. Consists of the following tests: Trail Making Test, Verbal Fluency Test, Design Fluency Test, Color–Word Interference Test, Sorting Test, 20 Questions Test, Word Context Test, Tower Test, Proverbs Test.
NAB Executive Module	Includes mazes, judgment, categories, and word-generation tasks.
Wisconsin Card Sorting Test	Used widely in clinical and research contexts; shorter 64-trial version available; examines problems with perseveration and ability for novel problem solving.
Category Test, Booklet Category Test, Short Category Test	From the HRNB; short version available; booklet version available but not recommended for use with the standard HRNB battery.
Trail Making Test, Color Trails Test, Comprehensive Trail Making Test	Attention, speed of information processing, and cognitive flexibility are measured.
Stroop Color–Word Test	Response inhibition aspect relates to executive functioning ability.
Cognitive Estimation Test	Examines the ability to make estimated judgments on everyday types of activities and items.
Ruff Figural Fluency Test	Design fluency is assessed; nonverbal equivalent to word fluency test.
Executive Control Battery	Executive dyscontrol; qualitative analysis of performance is assessed.
Iowa Gambling Task	Evaluates decision-making impairments related to frontal system damage. Emulates a gambling task of card selection and net earnings based on decisions made of card selection. Learning component is also included in the task.
Behavioral Assessment of the Dysexecutive Syndrome (BADS)	A multiple subtest measure geared toward obtaining ecologically valid data of executive functioning; includes a questionnaire of behavioral symptoms of executive functioning problems that can be filled out by the patient and by a collateral informant.

rehabilitated. A meta-analysis conducted by Kennedy et al.[60] reviewed 15 studies that met inclusion criterion for analysis and included studies that used metacognition strategy instruction as a method of executive function remediation. Their analysis showed promise for this method as well as for interventions that focus on verbal reasoning skill and multitasking training. Remediation of executive abilities may be difficult because high-level processes are required to benefit from interventions. Providing compensatory strategies for cognitive abilities that serve executive skills, such as assistance for complex attention, recent memory, and visuoconstruction deficits, will likely have an impact on the patient's net executive functioning capacity. Specific strategies for directly managing executive functioning ability often rely upon approaching the patient on many fronts. This includes providing consistent and continuous feedback (e.g., video- and audio-taped feedback, immediate feedback on tasks), structuring the patient's problem-solving approaches, and assisting the patient in organizing and simplifying the home or work environment.

There is considerable interplay between executive functioning and a person's ability for coping with everyday stressors and tasks. As studied by Krpan et al.,[61] executive functions are related to coping skills for individuals with TBI. Each individual varies to the extent and in what situations one may employ problem-focused coping (i.e., that involves planning, examination of solutions) or other forms of coping such as emotion-focused coping (handling stressors through regulating emotions). Not surprisingly, the Krpan study demonstrated that higher executive functioning was associated with use of problem-focused coping whereas poorer executive functioning related to emotion-focused coping, the latter of which the authors referred to as *escape avoidant* strategies of coping. For the rehabilitation professional who works with a person with TBI who demonstrates executive dysfunction, interventions that teach problem-solving skills, modeling of planning behaviors, and assist with improving self-monitoring skills will be beneficial. At the same time, it may be important to assist that person to learn and regulate emotions and use self-calming techniques and other ways to minimize the interference of escape avoidant behaviors. The authors go on to state the following:

> For example, a rehabilitation protocol might involve teaching people to use a conscious process to select adaptive coping strategies, how to effectively use emotion focused coping strategies, and perhaps even how to decode and adaptively respond to emotional or stressful stimuli (i.e., affective regulation) (p. 44).[61]

Component analyses of the task at hand (e.g., studying for a college examination) can reveal steps in which executive

dysfunction can impair (e.g., trouble with organization of study notes). These types of analyses may be used to identify strategies for remediation or compensation rather than attempting to find a treatment approach for executive abilities in general. Further strategies can be found in Eslinger[62]; Noggle, Dean, and Barisa[63]; and Oddy and Worthington.[64]

Mood and psychological functioning

> It's depressing, having to start all over and make sense out of the world you've lost because of injury and illness, to get these bits and pieces to add up to a coherent whole (p. xxi).[29]
>
> **L. Zasetsky**

Mood impairments and changes in personality and psychological functioning are commonplace after TBI. Although the assessment of mood states and interpersonal propensities are not considered neuropsychological variables in and of themselves, it is an essential element of the evaluation to understand the whole person. Clearly, mood disorders are common in TBI and may be a function of the neurobiology of neuropsychological disorder. One of the difficulties faced by clinicians in assessing mood after TBI is the fact that many measures rely on self-report (e.g., SCL-90, Center for Epidemiological Studies Depression scale, State–Trait Anxiety Inventory), and depending upon the patient's level of self-awareness and self-monitoring ability, the resulting scores may require adjustment and collateral input. Clinician-administered structured measures, such as the Hamilton Depression Scale, could also be employed to augment collateral data and other observational input. Clinicians using these measures are not likely to rely on one source of data to make determinations regarding mood.

Included within the larger concept of mood are dysphoria, anxiety, irritability, and anger as the primary four aspects of mood. The clinician evaluating mood components will often need to obtain and integrate information from multiple sources in order to best understand the patient's level and type of mood functioning. Self-report measures and the clinical interview (and careful monitoring of mental status variables during the interview), coupled with informant observations and questionnaires, can be an effective way of ascertaining mood in the person with TBI. Examination of mood fluctuations throughout a given day or week may be helpful to identify any diurnal patterns, situational circumstances, and interpersonal dynamics that may be contributory to mood presentation.

Personality and psychological functioning assessment requires more comprehensive instruments. Such assessments provide both state information (quantifying current mood states and conditions) and trait/personality information (quantifying enduring and pervasive interpersonal propensities and characteristics of the individual). Alteration of personality and psychological functioning, as was described at the beginning of the chapter in the Lanuti case, illustrates the impact of changed personhood in his psychosocial life. TBI can result in permanent changes in psychological and social functioning as a primary deficit (for example in frontal system injuries) and secondary to neurocognitive changes (e.g., memory and processing speed deficits that result in disrupted conversational prowess with friends and family). Table 31.10 lists some commonly utilized mood and psychological functioning measures.

ECOLOGICAL IMPLICATIONS

Mood dysfunction, including depression, anxiety, irritability and anger, can result in excess disability in psychosocial functioning and in cognitive functioning.[65] Treatment of depression can result in improved cognitive functioning as found by Fann et al.[66] The criteria for major depressive disorder includes concentration deficits, and its alleviation may, in turn, result in some cognitive improvement. In the patient with TBI, other neurobehavioral conditions, such as apathy and reduced affect regulation, may mimic depression, and such symptoms may overlap with depression. In either case, depression can be thoroughly assessed when utilizing multiple sources of data, including self-report (e.g., Beck Depression Inventory, Geriatric Depression Scale); structured interview formats (e.g., Hamilton Depression Rating Scale); and collateral observations by family, rehabilitation staff, and friends. Coping skills of the patient can moderate some of the effects of mood disorder in patients with TBI; however, the patient's capacity to employ psychological coping strategies may be dependent upon the intactness of executive abilities. Reduced self-awareness can act to reduce the frequency with which a patient may deem it necessary to change his or her own behavior and invoke coping strategies (e.g., use of positive self-statements in response to stressful situations). A combination of pharmacotherapy and psychotherapy may, therefore, prove beneficial to the patient who presents with mood disorder following TBI. Many patients with mood disorder find general mood benefits from physical reactivation through physical therapy and home exercise programs. Reengagement in pleasant activities[67] may also have a mood-elevating benefit. After TBI, the patient's ability to independently engage in community recreation and leisure pursuits may be limited. Postacute rehabilitation strategies that target recreation and leisure skill improvement will also have the added benefit of improving or maintaining euthymic mood. Other moderating variables that play a role in mood stabilization and cognition include chronic pain, sleep disturbance and fatigue, current medication regimen, and substance use—all of which should be assessed at the time of defining rehabilitation goals.

Clearly, changes in interpersonal functioning are distressing to family members, friends, coworkers, and others who knew the patient prior to TBI. Many an awkward moment can occur with others for the individual with TBI who presents with disinhibited social behaviors or mood regulation problems coupled with anosognosia. Interventions directed at modifying interpersonal transaction awareness and

Table 31.10 Tests of mood and psychological functioning

Test	Comment
Beck Depression Inventory/Beck Anxiety Inventory/Beck Depression Inventory Fast Screen for Medical Patients	Self-report measures of depression and anxiety (respectively); can sometimes be difficult in a severely cognitively impaired patient to complete.
Geriatric Depression Scale	Self-report measure of depression, normed for older adults; yes/no format.
PHQ-9	Self-report measure of depression including an additional item regarding the difficulty in work, home, and interpersonal ability secondary to depression symptoms.
Center for Epidemiological Studies Depression Scale (CES-D)	Commonly used in research; self-report represents a balance between mood, somatic, and cognitive aspects of depression.
Hamilton Depression Rating Scale	Used frequently in psychiatric research; structured interview results in clinician rating; a self-report version is available.
State–Trait Anxiety Inventory	Self-report measure that examines state anxiety and trait anxiety.
State–Trait Anger Expression Inventory–2	Measures various aspects of anger expression, including state anger and trait anger; an Anger Expression Index is provided.
Minnesota Multiphasic Personality Inventory–2 (MMPI-2/MMPI-RF)	Standard personality inventory that has been used extensively in TBI; measures mood states, coping, and interpersonal propensities.
Personality Assessment Inventory (PAI)	Comprehensive measure of mood, coping, interpersonal propensities, and treatment response indicators.
Millon Behavioral Medicine Diagnostic	Measures interpersonal coping methods in response to medical illness; assesses mood states and treatment responsivity indicators; rooted in Millon Theory.
Battery for Health Improvement–2	Measures biopsychosocial factors relevant to conceptualizing a patient's treatment.
Neuropsychological Impairment Scale	This questionnaire comes in two report forms: self-report and informant report. Measures aspects of perceived cognitive impairments, but also includes items related to affect, which may be playing a role in self-reported cognitive symptoms.
Neuropsychology Behavior and Affect Profile	Evaluates changes in personality and emotion after brain injury.
Neurobehavioral Function Inventory	Patient self-report and informant (family) report forms are available; includes depression, somatic symptoms, memory/attention, communication deficits, aggression, and motor deficit scales.
Neurobehavioral Rating Scale	Measures aspects of mood and behavior that represent consequences of brain injury.

behaviors may be predicated upon a comprehensive assessment of mood and interpersonal aspects of functioning.

AFTERWORD

One of the most frequently cited case studies of TBI is the tragic case of Phineas Gage, the railroad foreman who sustained a devastating penetrating head injury in 1848, when a tamping iron was driven through his left frontal lobe, secondary to a blast. Macmillan[68] documents some of the changes that Gage's physician, John Harlow, observed in his patient shortly after the accident:

> Remembers passing and past events correctly, as well before as since the injury. Intellectual manifestations feeble, being exceedingly capricious and childish, but with a will as indomitable as ever; is particularly obstinate; will not yield to restraint when it conflicts with his desires (p. 91).[68]

Gage experienced a dramatic change in his life of being a successful railroad worker to working as a side show for the Barnum and Bailey Circus, displaying the tamping iron and touted as "the only living man with a hole in the top of his head" (p. 98).[68] In an often cited paper, Stuss, Gow, and Hetherington[69] commented on Gage's change in personhood:

> Although he miraculously survived and demonstrated good physical recovery and many preserved cognitive abilities, his emotional behavior and personality were so significantly changed that his friends stated that he was a different person: "No longer Gage" (p. 349).[69]

This story has been repeated numerous times and is considered a classical case study in psychology[70] as well as prototypical to the changes observed after severe TBI, much like Case Lanuti as was described at the beginning of this chapter. Little has changed regarding common neuropsychological

and neurobehavioral outcomes in TBI. Today, we clearly know more about the specific neurobiological mechanisms of dysfunction and the functional brain mechanisms associated with neurocognitive function and dysfunction after TBI. Such refinements in assessment technology have allowed for more precise tracking of effective rehabilitation strategies. From Phineas Gage, we have a clear delineation of the task in front of rehabilitation professionals: to push not only for *care*, but to begin working toward *restoration* of function as was envisioned decades ago by Luria. In his book *Restoration of Function after Brain Injury*,[71] Luria surmised that there might be three hypotheses as to how recovery occurs after brain injury. First, evidence at that time pointed to the possibility that a temporary inhibition or inactivity occurred and recovery could be accounted for when that inhibition ceased. Second, in agreement with Kurt Goldstein's view, was that functions of the brain may not be as localized, and thus, there could be a process of "substitution" by other parts of the brain to compensate for the damaged portion. Third, the literature at the time he wrote his book pointed to the idea that there may be a "radical re-organization of the destroyed activity, in which after brain injury the deranged function is restored by means of entirely different neuronal structures, unaffected by the trauma" (p. xiii). It would be hoped that the neuropsychological evaluation may be a key method by which to understand restorative processes, accurately track changes in brain–behavior functions, and provide an opportunity for the clinician to use neuropsychological data in order to best define rehabilitation activities that truly have restorative value. Understanding the mechanisms that account for restoration led Luria to consider potential effective rehabilitation strategies, which certainly defined much of his professional career in neuropsychology, behavioral neurology, and as a cultural psychologist. Hopefully, neuropsychology as a field can contribute to this endeavor, not as an end, but as a means to an end for restoration after brain injury. Luria writes,

> Only after these problems are solved does it become possible to develop, on a firm theoretical foundation, a rational system of restorative therapy which takes into account the pathogenesis of the particular disorder and provides rational methods of influencing the various links of this complex system (pp. xiii–xiv).[71]

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32

Neurobehavioral consequences of mild traumatic brain injury in military service members and veterans

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INTRODUCTION

Traumatic brain injury (TBI) is a continuing concern for military treatment facilities operated by the Department of Defense (DoD), the Veterans Health Administration (VHA), and civilian health care providers who deliver services to U.S. active duty service members and veterans. Improvements in body armor and other protective gear worn in the combat environment have dramatically increased the likelihood of survival after blast exposure and other related injuries. Blast-related exposures and other mechanisms of sustaining TBI in both the deployed and nondeployed setting can be the source of an array of physiological, neurocognitive, and psychological disorders in military service members and veterans. The goals of this chapter are primarily threefold: 1) to describe common aftereffects of blast-related exposures in military personnel and other events that produce TBI, 2) to describe the many co-occurring disorders that complicate the medical and psychological symptom picture for those who have had blast exposures and deployment to war zones, and 3) to discuss the current approach for polytrauma rehabilitation and integrated care for U.S. active duty service members and

veterans who have served in Operation Enduring Freedom (Afghanistan 2001–2014), Operation Iraqi Freedom (Iraq 2003–2011), and Operation New Dawn (Iraq 2011–present), hereafter referred to as OEF/OIF/OND. This chapter also focuses on mild traumatic brain injury (MTBI) as opposed to those who suffered moderate and severe TBI, given that the vast majority of military TBI falls into the mild category. In addition, this chapter underscores the clinical situation of "polytrauma" as relevant to military and veteran populations given the high frequency of co-occurring disorders that are seen in military and veteran treatment environments.

TBI IN MILITARY ENVIRONMENTS

The phenomena of brain injury sustained in war are recorded in the historical literature as far back as wars have been documented. The nature of combat environments is sometimes difficult to imagine by a person who has not served, and thanks to modern medical surveillance methods, service members are now tracked to a great extent with regard to injuries sustained both in deployed and nondeployed settings. With greater surveillance comes a better understanding of the multiple co-occurring conditions that occur while serving in the military, and therefore, polytrauma has become a more accepted terminology to describe the host of injuries that can occur while a person is on active duty and often carry through in their health care as a veteran.

A brief history of brain injury and co-occurring symptoms in war

Blunt head trauma and penetrating head wounds occur due to the multiplicity of exposures that can occur in the war zone. For service members who have been engaged in combat since the time of the U.S. Civil War (as well as throughout recorded history) much has been written and learned about the consequences of injuries sustained in combat settings. Spawned by World War I, a significant amount of literature both in Great Britain and the United States was written that provided accounts of war injury, TBI, and concepts that we know today as posttraumatic stress disorder (PTSD).

A historical review of the concept of "shell shock" by Jones, Fear, and Wessely[1] discusses the early phases of battle during World War I being characterized by significant exposures to blast explosions with consequent head and brain injuries. Immediate postconcussion symptoms were present, and persisting symptoms that were not explainable by organic lesions began to be referred to as shell shock. The authors go on to describe how the British government awarded pensions for some 32,000 soldiers for shell shock by 1918, and increasing numbers of soldiers were subsequently pensioned for the disorder. As the concept evolved, both physiological and psychological aspects of shell shock were recognized, much akin to what is ascribed to the phenomenology of postconcussion syndrome and PTSD. Interestingly, as described by Salmon[2], there was a considerably higher rate of war neuroses among officers when compared to men at the front of the war. He notes the following:

> The ratio of officers to men at the front is approximately 1:30. Among the wounded it is 1:24. Among the patients admitted to the special hospitals for war neuroses in England during the year ending April 30, 1917, it was 1:6. (p. 29)

Salmon goes on to describe how those with injuries to the brain and spinal cord did not have a high prevalence of war neuroses. He also had an objection to the term "shell shock" as it implicated an instantaneous occurrence of neurotic behavior. Despite these objections, shell shock was invoked in subsequent war conflicts around the globe, the term even referred to in modern day media with reference to a unique form of brain injury resulting from blast exposure. A recent article in *National Geographic* magazine[3] described how the concept of shell shock during World War I was more akin to emotional reactions to traumas experienced in combat whereas the science of blast exposures has advanced to be able to describe the impact of the physics of such exposures on the brain.

Others, such as M. D. Eder,[4] chose to use the term "war shock" to describe neurotic reactions to combat exposures and experience. He describes his experience with British soldiers who fought in the Gallipoli campaign and who returned with various neurotic symptoms, including diagnoses of conversion hysteria, anxiety hysteria, and psychasthenia. Each of these psycho-neuroses was conceptualized as a functional disorder in the sense of creating disablement although differentiated from functional impairment produced by central nervous system lesions. He notes the following:

> The term functional disease is a very good one if it be understood that we have primarily an interference with function, which may or may not produce secondarily a structural change. This is in sharp contrast with organic diseases where the primary lesion is structural, the interference with function being secondary. (p. 5)

In World War II, the concept of "war neuroses" was described by Kurt Goldstein, a German neurologist and psychiatrist who is thought of as one of the founders of modern neuropsychology and a founder of developing methods of neurorehabilitation. He is well known for his work in evaluating and developing early cognitive rehabilitation approaches for soldiers who sustained combat-related TBI with the publication of his book titled *After Effects of Brain Injuries in War*.[5] During that same time era, Goldstein[6] described "catastrophic behavior" that occurred in soldiers who sustained brain injuries with anxiety and fear being a root cause of these reactions and results in the context of being on the battlefield. Goldstein talked about three types

of "nervous breakdown due to war conditions," including 1) acute anxiety states, 2) that characterized by conversion symptoms, and 3) exacerbation of previous neuroses by being in the combat war theater. Many of Goldstein's descriptions of these catastrophic reactions are today familiar as symptoms of PTSD. As is discussed later, the overlap of symptomatology of MTBI with PTSD and depression may represent the modern equivalent to the shell shock phenomena of past war conflicts. Although these war-related phenomena seem not to change across history, changes in terminology do occur.

MTBI in the context of polytrauma and co-occurring disorders

The term "concussion" is frequently used in reference to OEF/OIF/OND service members and veterans who experienced an event that leads to immediate concussive symptomatology (e.g., being dazed, amnestic, brief loss of consciousness) and may be a result of various mechanical forces or, in the deployed setting, also due to blast-related forces. However, it should be noted that in the scientific literature regarding war-related injuries in military and veterans, the terms "concussion" and "MTBI" are frequently used interchangeably.

The Defense and Veterans Brain Injury Center (DVBIC), an organization subsumed under the Defense Center of Excellence for Psychological Health and Traumatic Brain Injury (DCoE), maintains a database regarding the current prevalence of TBI among active-duty service members in the DoD.[7] This database is derived from statistical data obtained in cooperation with the Armed Forces Health Surveillance Center. As of the first quarter of 2015, since the year 2000, there have been a total of 327,299 who have sustained a TBI, of whom 269,580 (84%) fall in the MTBI category. There have been 4,865 with penetrating brain injury, 3,422 who fall in the severe TBI category, and 27,728 who fall in the moderate TBI range. It is very important to note that, according to the DVBIC report, *80% of those who have sustained TBI occurred in the nondeployed setting.* Common causes of those in this 80% category of injury were due to motor vehicle accidents, sport and recreation incidences, falls, and military training activities.

In the other approximately 20% of those with TBI, injury occurred in the deployed environment, and similar to prior wars, blast exposures continue to be an unfortunate mechanism of injury. In this regard blast-related injuries in OEF/OIF/OND largely occur as a result of exposure to explosive materials and devices, including car/truck bombs, land mines, rocket-propelled grenades (RPGs), mortar rounds, suicide bombers with explosive vests, and other improvised explosive devices (IEDs). Vehicle-borne IEDs (VBIEDs) involving the packaging of enormous amounts of explosives and other materials that can act as damaging shrapnel were common in these war theaters. These and other devices can create significant overpressurization waves and secondary damage that can result in the service member experiencing a blast-related TBI. They continue to be used by insurgents who fight with local police and military forces in these war zones. Blast exposures can result in a host of outcomes as noted, and these are explained later in this chapter.

Many of the results of blast exposure can produce symptoms that persist beyond the time of separation from the military and are seen by providers within the VHA. Such symptoms can be cumulative given the nature of combat experiences in which multiple blast exposures with consequent concussions may occur. Some caution is necessary to note the attribution of symptoms postdeployment and active-duty status in that the situation of multiple medical and psychological comorbidities may, on the surface, appear to be blast exposure-related or possibly attributable to a concussive event. Howe[8] cautions the clinician to not only be aware of the various mechanisms and outcomes of blast exposure, but also to place potential postconcussion symptoms within the context of other "co-occurring complexities," such as chronic pain, sleep disturbances, PTSD, substance abuse, and other conditions.

The clinical presentation of polytrauma often results from the cumulative impact of several co-occurring disorders, of which TBI and blast exposure may be a part. The current definition of polytrauma according to the VHA is as follows:

> *Polytrauma* occurs when a person experiences injuries to multiple body parts and organ systems often, but not always, as a result of blast-related events. TBI frequently occurs in polytrauma in combination with other disabling conditions, such as amputation, burns, spinal cord injury, auditory and visual damage, spinal cord injury (SCI), post-traumatic stress disorder (PTSD), and other medical conditions. Due to the severity and complexity of their injuries, Veterans and Service Members with polytrauma require a high level of integration and coordination of clinical care and other support services.[9]

Although we appreciate the importance of blast-related injury globally, the focus of the present chapter is on blast-related brain injury sustained by active-duty service members and veterans of OEF/OIF/OND. Military personnel differ in several important ways from their civilian counterparts. Even in peacetime, rates of TBI are elevated among military personnel. Men in the military have 1.6 times the rate of TBI as their civilian counterparts, and women in the military have 2.5 times higher rates of TBI than civilian women.[10] During war, the incidence of TBI increases with closed head injuries remaining the most prevalent (compared to penetrating head injuries). In a recent study of 2,525 soldiers who were 3–4 months postdeployment (59% response rate), Hoge and colleagues[11] found that service members who report MTBI were more likely to have experienced high combat intensity, be injured in a blast, have

multiple blast exposures, be hospitalized during deployment, and be younger males of junior rank.

Differences between OEF/OIF/OND and other war conflicts

The nature of combat characterizing OEF/OIF/OND differs in several significant ways from previous conflicts, which likely contributes to the elevated incidence of brain injury in the current military and veteran population. The *first factor* that accounts for differences is that, in the current conflicts, unique methods of attack and weaponry are being used by enemy combatants. The widespread use of the IED in Iraq and Afghanistan and also used in terror attacks across the globe and on U.S. soil (e.g., the Boston Marathon bombing on April 13, 2013, in which pressure cooker bombs were used) can account for many multisystemic injuries. As a measure of the intensity of blast exposures, more than 10,000 such attacks were reported in Iraq during 2005 alone.[12] This latter study reported that, of 100 consecutive causalities sustained by coalition forces in January 2006, 53 of these were due to IED explosions across 23 incidents. Of note is that 21 of the 23 incidents that resulted in casualties were caused by explosively formed projectiles (EFP), known for their high kill rate. In another study by Holcomb et al.[13] of the deaths among U.S. Special Forces service members who died between October 2001 and November 2004 (n = 82), 43% were caused by explosions, followed by 28% being fatally wounded by gunshot wounds. According to the U.S. Joint Theater Trauma Registry for injuries accounted for in OEF and OIF between October 2001 and January 2005, blast explosions accounted for 75% of the mechanisms of extremity wounds.[14] Out of a total of 1,566 service members, 6,609 wounds were recorded, and of these, 54% of these soldiers sustained extremity wounds. This figure is noted to have been consistent with previous wars (WWII, Korea, Vietnam, Operation Desert Storm).

The *second factor* contributing to the elevated rates of injury secondary to blast explosions is likely due to the fact that service members survive their injuries today more frequently than in previous wars. Kevlar body armor provides improved protection of vital body organs from penetrating shrapnel fragments and other material dispersed by high velocity overpressurization waves created by blast explosions. The armor on combat vehicles differs somewhat by vehicle model and purpose with some vehicles able to survive driving over an IED and others that are relatively more vulnerable. Medical support for troops is faster, more mobile, and closer to battle than has historically been the case, providing the ability to both rapidly treat and evacuate injured troops. As a result of improved armor, approximately 10% of those wounded in OEF/OIF sustained lethal war wounds, compared to 24% in the Persian Gulf War of 1990 to 1991, 24% in Vietnam, and 30% in World War II.[15]

The *third factor* contributing to the elevated rates of blast-related injuries are changes in military operations. As described in the often-cited RAND report,[5] the conflicts in Iraq and Afghanistan represent the most sustained U.S. combat operations since the Vietnam War. In fact, OEF is now the longest sustained military operation in U.S. history. Many of those who served in OEF and OIF experienced extended lengths of tours as well as serving multiple tours of duty in the combat environment. These factors led to increased physical and psychological stress among military service members. Additionally, many of those who served in OEF and OIF were from the Army and Navy Reserves and Army National Guard units who served in infantry roles. Due to the nature of operations in Iraq and Afghanistan, it is in these infantry roles that many of the blast-related injuries occur.

Overview of the context and case definition

There are (at least) two issues that make blast-related TBI, especially of "mild" severity, unique from other types of MTBI. First, blast-related TBI frequently occurs in a complex context, notable for high rates of comorbid physical injuries, the probability of repeated blast exposure and injury, and the physical and psychological stress associated with the theater of combat. Second, the physiological mechanisms of blast-related TBI may be meaningfully distinct from MTBI due to the blunt trauma mechanisms seen more typically in civilian settings. Blast-related TBI less frequently results in severe TBI, and many service members returning from the war theater report multiple blast exposures, many that are associated with immediate postconcussive symptomatology, and any one of these concussive events could be considered a MTBI. However, blast-related MTBI may differ in outcome from TBI due to the presence of other co-occurring conditions and, thus, may moderate predictions of recovery that are commonly associated with the natural recovery from a single civilian MTBI. The context within which these MTBIs or multiple concussions occur, along with co-occurring conditions, such as combat-related PTSD, depression, chronic multisite pain disorders, and the presence of sleep disorders and fatigue, differentiate OEF and OIF blast injury from that seen in the civilian world.

MTBIs are usually classified as injuries resulting in loss of consciousness (LOC) up to 30 minutes and posttraumatic amnesia (PTA) up to 24 hours, and for most, recovery is fairly complete and rapid, occurring within 3 months of injury. TBI of moderate severity, on the other hand, is characterized by LOC of up to 6 hours and PTA ranging between 1 to 7 days, and the typical recovery trajectory is more gradual, more prolonged, and less likely to be characterized by a complete return to baseline function. Note, in the present chapter, we interchangeably use the terms MTBI and concussion, and we do not differentiate between concussions of different grades.

Differences between military service-related and civilian MTBI

Within active duty and veteran populations, the term "mild traumatic brain injury" is relatively diffuse and can be

applied to combat-related, blast-exposure, and noncombat TBI. Although similarities have been drawn between the sports concussion literature and military concussions,[16] service-related MTBI differs from that in the civilian sector due to contextual issues, such as environment, co-occurring injuries, psychological trauma, and military tactical priorities. There are numerous extreme environmental exposures related to military service that may affect the general health status of a concussed service member, such as dehydration-inducing climates, biological toxins, or radioactivity due to exposure to depleted uranium. Additionally, active duty service members and veterans presenting with a history of MTBI have often sustained other service-related injuries that can contribute to chronic musculoskeletal, neuropathic, and, in some cases of those with amputations, phantom limb pain. Military concussion also differs from civilian MTBI in that combat-related injuries frequently occur within the context of the psychological trauma of warfare (e.g., killing, witnessing deaths, having one's life threatened in unpredictable situations). Overall, superimposing an MTBI on other physical and mental health risks may result in different outcomes, and therefore, it may not be appropriate to simply translate the expectation of recovery for a single civilian MTBI to military personnel whose health status may be affected by other war theater exposures.

Military culture, ethos, and priorities also vary from those of the civilian sector, and as such, the immediate treatment of MTBI similarly differs. Transnationally and throughout eras, military culture is broadly characterized by its communal orientation, hierarchical structure, and focus on discipline.[17] Central to U.S. military service is the practice of living by a "creed" or set of virtues. Within the United States, new military recruits formally learn overarching values to guide their service that differ depending on military branch. These values may include loyalty, commitment, duty, and service before self in addition to the concept "leave no one behind" (SAMHSA[18]). For example, most active duty soldiers and veterans who served since 2003 can state the Warrior Ethos from memory: "I will always place the mission first. I will never accept defeat. I will never quit. I will never leave a fallen comrade" (quoted from the 2003 U.S. Army Warrior Ethos). Given the salience of military culture, immediate priorities following MTBI often depend on a service member's role, mission, and comrades-in-arms. Within the military, from a tactical stand-point, medical care has three goals: 1) treat the casualty, 2) prevent additional casualties, and 3) complete the mission.[19] The tactical priorities of the mission often make recommended care following MTBI difficult, and furthermore, military culture may influence service members to under-report injury following MTBI.

There are a number of empirical differences between civilian MTBI and service-related MTBI (noted in Table 32.1). For example, when a service member is in the midst of a fire fight or when mortar rounds are landing nearby, it would be difficult to ascertain information such as a Glasgow Coma Scale (GCS) score (something that might be assessed by a paramedic or emergency medical technician [EMT] in the civilian sector), and therefore, early head injury index information is often absent when trying to judge the level of injury several months later by retrospective report. If the service member sustains an injury severe enough to be medically assessed in the combat support hospital (CSH), early head injury indices may be obtained and deemed useful for later determinations of TBI diagnoses and rehabilitation. It is also unclear, at present, to know the extent to which multiple concussion outcomes are affected by the superimposition of a dysregulated hypothalamic–pituitary–adrenal (HPA) axis secondary to significant sleep deprivation, maintaining high alert levels, and exposure to multiple stressors. These are but a few of the differences between civilian MTBI and combat-related MTBI that cautions the health care provider in completing assessments and developing plans of care for these service members.

Classification of blast-related injuries

In order for someone to even be considered as having experienced MTBI, he or she must have experienced some event, such as a blast exposure, fall, or blow to the head or body that constitutes a plausible cause of such injury. Exposures to blast waves can have many effects on the body and brain

Table 32.1 Differences between civilian and combat-related MTBI

Civilian MTBI characteristics	Combat-related MTBI characteristics
• Single incident TBI	• Multiple concussive events; cumulative injuries
• Most occur as a result of a motor vehicle accident, fall, or assault	• Blast-related exposures, falls, motor vehicle accidents—sometimes, all three mechanisms occur in a single incident
• Common to have immediate medical response, EMT evaluation, hospitalization, prescription of rest with slow reactivation ideal, access to outpatient rehabilitation if funding allows	• Immediate medical evaluation in the combat environment is sometimes difficult; new in-theater protocols in place to allow for evaluation and graded return to duty; increased HPA axis activation common
• Resolution of neuropsychological symptoms within 1 to 3 months	• Co-occurring exposures prolongs recovery
• Many are in litigation	• Desire for return to duty and redeployment

and result in physical and cognitive impairment. It should be noted that exposure to a blast wave does not necessarily result in a TBI. However, knowing the mechanisms of injury related to blast exposure can further place the symptoms into a context.

Each explosion creates a blast wind that will travel in excess of 1,000 miles per hour. As illustrated by Taber, Warden, and Hurley,[20] peak overpressurization of the blast wave will occur fairly immediately after the explosion. This is followed by a negative pressure wave that results in air flow pressure back toward the origin of the explosion. A second but smaller pressurization wave can also occur as a third phase of the blast wind process. It should be noted that, depending upon the type and magnitude of the blast explosion, the blast wind can reach a velocity capable of creating a traumatic amputation or eye enucleation. This is just to underscore the pernicious nature of blast wave exposures and the prominent aftereffects on the human body. The physics of a blast exposure are such that the blast wind and overpressurization force will affect the air and fluid-filled organs of the body (e.g., lungs, ear canal, stomach, and colon). The blast wind can be powerful enough to propel a service member a significant distance from the explosion, depending on how close that individual was from the source of the blast. Displacement by the wind can then result in a fall or other blow to the head by being thrown into objects or have other material fall on the body. Blunt and penetrating wounds to the body can also occur secondary to blast wave exposure. Although Kevlar body armor is protective of ballistic projectiles and shrapnel penetrating injuries in the regions most protected by the body armor (e.g., trunk, back, shoulder to waist), the body armor does not protect against pulmonary overpressure wave effects and potential for pulmonary acute gas embolism.

Blast-related injuries, including those that cause TBI, are categorized into primary, secondary, tertiary, and quaternary types, depending on the mechanisms, according to the Centers for Disease Control and Prevention (CDC).[21] Table 32.2 provides the classification of blast-related injuries along with examples of such injuries at each level.

Clinical and diagnostic considerations in combat-related MTBI

In contrast to the presentation of MTBI in civilian settings, the presentation of troops who sustained blast or combat-related TBI tends to be complicated. Personnel who sustain concussive injuries in combat may be unaware that their brief loss of consciousness or altered mental status, in fact, may constitute an injury requiring medical evaluation. Moreover, soldiers with basic combat life-support training are taught to assess for and prioritize aid for persons with life-threatening injuries. Transient alterations in mental status are relatively lower priority injuries and frequently ignored due to the necessity of the situation. Presentation is further complicated by the frequent presence of comorbid physical injuries (polytrauma) that may have been incurred in the same event causing MTBI or in the same deployment. For example, in a study of OEF/OIF patients evacuated from combat to Walter Reed Army Medical Center (WRAMC), 28% had a TBI and, of those, 19% had a concomitant amputation.[22] The majority of persons seen with TBI at WRAMC had experienced closed head injury (88%), and less than half were mild in severity. In a related vein, the probability of repeated blast exposure and concussion, both prior to and during deployment, must be considered as part of the context in which blast injury occurs. On interview, it is critical to establish as accurately as possible not only the number of concussive events, but also their approximate dates and relative temporal separation from each other.

Common methods of grading the severity level of blast-related and other combat-related TBI can be applied although, as noted earlier, such application is done with caution. Once the presence of a plausible mechanism of injury is established (e.g., blast-wave exposure, including being thrown from the site of the blast with consequent blunt

Table 32.2 Classification of blast-related injuries with examples

Blast injury type	Mechanism of injury	Consequences
Primary	Overpressurization wave	Tympanic membrane rupture, pulmonary injury and "blast lung" effects, ruptures of the viscus and viscus injury, traumatic amputation, eye enucleation/rupture of the eye globe, associated with dyspnea and chest pain after blast exposure, injury to air and fluid-filled organs
Secondary	Projectile, fragments, debris, particulate matter	Penetrating wounds, fragment injuries and shrapnel injuries, blunt trauma to the head and body
Tertiary	Displacement of the person by blast wave, structural collapse of buildings or nearby structures	Blunt and penetrating trauma, acceleration and deceleration forces to the head/brain by being thrown into stationary objects, traumatic amputation, fractures, crush injuries
Quaternary	Illnesses, injury, and diseases and conditions due to explosive-related exposures	Burns, asphyxia, toxic exposures and inhalation, worsening of existing diseases (e.g., asthma), exposure to depleted uranium, chemical exposures

head trauma), the presence of certain immediate symptoms is central to defining initial head injury severity. *It is important to note that defining initial head injury severity is separate from determining what may be producing persisting neurobehavioral, physical, and cognitive problems in the active-duty service member or veteran*. Although there continues to be discussions regarding uniform definitions of MTBI,[23] clinicians who are tasked with determining by retrospective reporting by the patient will frequently employ the American Congress of Rehabilitation's definition of MTBI,[24] the American Academy of Neurology Practice Parameters on concussion,[25] and screening questions that assist in case identification for consideration of MTBI developed by the Defense and Veterans' Brain Injury Center.[26,27]

Using the ACRM criteria includes identifying a plausible mechanism of injury that results in immediate and transient focal neurological deficits, including LOC or altered mental status lasting 30 minutes or less and any loss of memory for events immediately before or after the accident (but not exceeding 24 hours). Such information is not readily available in the war theater, and much of this type of information is gathered retrospectively by service member or veteran self-report. Reliance on self-report alone may be insufficient to establish a diagnosis of MTBI, and extensive information gathering around concussive events is important. Establishing type of explosive device (e.g., IED, VBIED, mortar round, RPG) to which the service member was exposed, how close in proximity that person was to the explosion, the extent to which there was displacement of the body away from the explosion, and whether or not there was blunt head trauma are important variables to ascertain. It may be helpful to know about immediate symptoms after the explosion, such as feeling dazed or disoriented. However, such experiences reported by the service member or veteran may be due to non-neurological factors, such as being startled by an explosion and being in the midst of a fire fight that can be disorienting, stressful, and confusing.

Concussions can be graded by the AAN practice parameters, and technically differentiated into three levels of severity. Grade I concussions are characterized by transient confusion, no LOC, and symptoms of mental status abnormalities that resolve within 15 minutes or less. Grade II concussions are also defined as transient confusion and no LOC, but symptoms persist for longer than 15 minutes. Grade III concussions are characterized by LOC up to 30 minutes. All grades of concussion are technically considered to be MTBI. Again, these variables may be obtained by self-report and are less reliable as the sole source of information to determine head injury severity.

A range of postconcussion symptoms can emerge within the first 48 hours of injury. The most common physical symptoms include headache, dizziness, nausea or vomiting, fatigue, noise or light intolerance, and insomnia. These physical symptoms may result in the service member being seen at the CSH where a diagnosis of concussion may be made. Cognitive complaints are usually evident within 1–2 weeks and include memory complaints and poor concentration. Emotional or psychological symptoms, which also emerge within 24 to 48 hours of injury, include depression, anxiety, irritability, or mood lability. These problems may not be readily reported by the active-duty service member for a variety of reasons, including the need and desire to continue to perform his or her duties in the theater, potential stigma in reporting psychological symptoms that may arise secondary to postconcussion symptoms, and the belief that symptoms will abate eventually with the attitude of "pushing through" minor or persisting symptoms.

Symptoms tend to be most apparent immediately after the blast event with significant variability in the resolution depending upon whether the service member continues to serve in a high combat–intensity environment and exposure to further blasts or other mechanism of head injury and may also depend on the extent to which that service member seeks help for symptoms. Severity of symptoms of MTBI is also in proportion to the severity of the initial injury. For example, a service member might describe being hit by a mortar round that exploded 10 feet away with no recollection of being thrown several feet from the blast into a concrete barrier with immediate experiences of being dazed and disorientated. Immediately afterward, that service member may describe having trouble carrying out their duties or being told by other unit members that cognitive problems (e.g., repeating information, memory problems, difficulty carrying through on tasks) were noticeable after the blast exposure. In this case, the clinician may suspect that a concussion may have occurred. Others might describe being near a VBIED (e.g., 50 yards away) and feeling the overpressurization wave but without any immediate symptoms. The latter scenario is not likely to have produced a concussion. There is no symptom that is unique to or diagnostic of MTBI in the combat environment. In addition, in the case of the active-duty service member or veteran, co-occurring conditions may complicate the clinical picture. Thus, it is difficult to draw direct connections between symptom complex and diagnosis.

ASSESSMENT OF SERVICE-RELATED TBI

Beginning in April 2007, the VHA[28] implemented a routine primary screen for TBI. Comprised of the following four questions, the VHA screened for 1) the presence of an event that could plausibly cause TBI (blast or explosion, vehicular accident, fragment wound or bullet wound above the shoulders, fall); 2) any immediate symptoms around the event (losing consciousness or being "knocked out;" being dazed, confused, or "seeing stars;" not remembering the event); 3) beginning, or worsening of, symptoms after the event (memory problems or lapses, balance problems or dizziness, sensitivity to bright light, irritability, headaches, sleep problems); and 4) current problems within the past week (including the same set of symptoms noted in #3). Screening positive on all four items automatically triggered a referral for more in-depth evaluation. This next level of evaluation, known as the *Comprehensive TBI Evaluation*, is conducted

by a licensed medical practitioner (MD, DO, PA, ARNP) and frequently done in tandem with a psychologist (clinical psychologist, rehabilitation psychologist, neuropsychologist). The goal of the TBI Secondary Evaluation is to more definitively diagnose the veteran, including TBI, PTSD, and other co-occurring conditions and develop a rehabilitation plan of care.

Interview as the gold standard for assessment

Diagnosing MTBI after the fact and against a backdrop of myriad competing plausible etiological factors is fraught with challenges, yet it is a typical referral question among providers within the DoD and the VHA. The goal of this section is to outline concrete assessment strategies to aid the clinician in differential diagnosis and treatment planning. It is our impression that there is no substitute for an in-depth interview in understanding a possible history of blast injury.

Before outlining the specific components of an interview, we would like to suggest some general factors to consider. First, a brief caveat about interviewing persons who have served in recent combat: clinicians working with this population are strongly encouraged to obtain some basic familiarity with the unique language employed by military personnel so that they can establish credibility and rapport with the patients. For example, familiarity with terms and abbreviations related to rank, job duties, geographical locations, weapons, equipment, operations, and vehicles will greatly enhance the interviewee's comfort and likelihood of the interviewer obtaining accurate information. Second, it should also be emphasized that the context of the interview is important. Anecdotally, many service members have reported to us that they have denied symptoms of TBI in certain interview contexts (e.g., routine postdeployment evaluations) because of fear of this diagnosis interfering with their expedient return home or with future promotions. Thus, it is important to explain the purpose of the evaluation and assess up front any misconceptions or concerns the patient may have about undergoing such assessment. Third, it should be clarified that the following domains of assessment (event details, immediate and persistent symptoms) need to be evaluated for each and every blast event that occurred. Once this is completed, a systematic assessment of the following components can begin.

BLAST OR INJURY-INDUCING EVENT

To evaluate for the presence of a blast that could plausibly cause a brain injury, several questions are recommended to fully appreciate the mechanism, including 1) type, size, and estimated amount of explosive; 2) proximity of blast to patient and orientation of patient to the blast (i.e., facing the explosion directly vs. having one's back to it, height and direction of the blast force); 3) protective or buffering layers between patient and explosion (i.e., in a building or vehicle versus exposed on foot); 4) presence of protective gear (e.g., helmet, protective eyewear, ear plugs); 5) associated secondary, tertiary, quaternary, and quinary mechanisms of injury; and 6) other physical evidence to help gauge force, such as damage to proximal vehicles and buildings, injuries to others nearby, and displacement from the site of the explosion. The clinician should also pinpoint the date of each blast injury, if possible, to allow for evaluation of the effect of cumulative exposure. Without a plausible mechanism of injury or blast event, the diagnosis of TBI cannot be made.

Immediate symptoms after TBI in combat theater

Although it is critical to evaluate the immediate symptoms of TBI (altered level or LOC, peritraumatic amnesia), this may be difficult to accomplish as the patient may be unaware of whether or not they had a period of LOC and, if so, to know the duration. This is especially true if the event was unwitnessed and the patient regained consciousness by the time he or she was evaluated. Moreover, patients who regain consciousness during a combat situation are frequently immediately forced into action and are unable to assess or attend to any symptoms they may be experiencing in even a cursory way.

In assessing loss of or alteration in level of consciousness, multiple questions and a flexible approach may be beneficial. Obvious questions, such as "Did you lose consciousness after this event?" may be difficult for the patient to answer due to amnesia around details of the event or lack of understanding of the true meaning of LOC. Alternative ways of interviewing patients about such events may include having the patient describe the event in as much detail as he or she can remember, including things he or she heard, saw, experienced, thought, or did. Assessing altered mental status accurately may need to be differentiated from psychological shock or confusion after a blast. To differentiate confusion or shock due to trauma, combat, or simply proximity to a large blast, we recommend asking detailed questions to ascertain the degree to which the patient is able to provide a continuous detailed account of the event. If he or she has gaps in his or her memory or periods for which he or she cannot account, the clinician may be more confident in surmising an altered level of consciousness was likely. Similarly, in assessing PTA, multiple interview questions may be necessary to truly appreciate breaks in continuous memory. Service members may have retroactively received information about blast events from their fellow soldiers, and this needs to be differentiated from their own memory of the event in real time. PTA is strictly defined as the time interval from the impact until the patient is able to form memories for ongoing events continuously. During PTA, the person is not fully oriented or able to remember information after a period of distraction. Ways to ask about this include phrases such as "Please tell us, moment by moment, what happened after the blast," with repeated requests for more detail until the examiner is reasonably confident that the time is plausibly and completely accounted for (or

clear gaps are identified). The interviewing provider is also encouraged to ask the patient about information he or she received after the fact from others who might have witnessed the event.

Responsiveness and behavior immediately after the event, which in the civilian world is often measured by EMTs and paramedics using the GCS and reported in the field notes, are rarely available. Interviewers are encouraged to ask questions that mirror GCS domains that allow them to appreciate responsiveness and behaviors after the event. For example, one might ask about motor responsiveness ("Could you move about voluntarily? Were you able to continue doing your mission? Did you notice any physical changes in your ability to move?") and verbal responsiveness ("Were you able to understand other people immediately after this happened? Could you say what you wanted to say? What, if any, changes did you notice in your ability to talk or understand others?"). Some of these direct questions may be unnecessary if the patient provides an account of sufficient detail that it is apparent that he or she was fully responsive and engaged.

POSTCONCUSSION SYMPTOMS

Signs and symptoms of TBI that typically emerge within 48 hours of injury (or sooner) can include headaches or neck pain; lightheadedness, dizziness, or loss of balance; nausea; insomnia; tinnitus or ringing in the ears; sensitivity to light or sound; difficulty remembering, concentrating, or making decisions; slowness in thinking, speaking, acting, or reading; getting lost or easily confused; feeling irritable; or experiencing changes in mood or personality. The interviewing clinician is encouraged to systematically assess for the presence of these symptoms in the days following the blast injury. Related to this, the interviewing clinician should also inquire about any medical attention that was sought and the outcome of that effort as well as any other behaviors that were required to cope with symptoms. For example, inquire about use of over-the-counter medication, the need for extra rest, the need for any compensatory strategies that were identified, and any feedback from superiors or other service members. The clinician is also advised to ask about the effect of the injury on the service member's ability to perform his or her duties in the days or weeks after the event, recognizing that, even though rest or other postconcussion treatment measures may have been indicated medically, these may not have been realistically available options in the combat zone.

Assessment of current cognitive and neurobehavioral symptom complex

For a majority of civilians, postconcussion symptoms tend to resolve rapidly with full restoration of preinjury function expected within 3 to 6 months. Those with symptoms that persist beyond 6 months may be experiencing a persistent postconcussive syndrome. It is unknown whether this trajectory is also true for those with blast-related injury whose co-occurring conditions may, in fact, slow or complicate recovery to baseline levels of functioning. As part of the TBI Secondary Evaluation, the VHA employs the Neurobehavioral Symptom Inventory (NSI)[29] to assess current symptoms. The spectrum of symptoms contained on this questionnaire allows the clinician to probe in greater depth regarding the patient's experience and functional limitations that may be due to reported symptoms. Clusters of symptoms can be examined on this questionnaire, which can also provide hypotheses regarding potential overlap of concussion and mental health conditions. For example, emotional symptoms that appear on the NSI may be secondary to the presence of PTSD or depression. It is conceivable that emotional symptoms of concussion could be enhanced by PTSD or depression, and by the same token, the severity and persistence of PTSD or depression may be complicated by the concussion. In sum, the clinical evaluation of the OEF/OIF service member or veteran must take into account not only the individual diagnoses, signs, symptoms, and conditions that are presented, but also appreciate the interactive elements when there are multiple co-occurring conditions; hence, the term *polytrauma* has been employed and is characteristic of this new population of injured military personnel and veterans.

CO-OCCURRING DISORDERS AND MTBI

Several salient aspects of the psychosocial environment surrounding service-related MTBI should be considered. Combat zones are stressful and physically demanding arenas in which to carry out operations and to accomplish missions as directed by military command. This unique environment drives the divergence between civilian settings of TBI and those acquired during military service. Active-duty service members are exposed to an array of stressors and traumatic experiences that would be highly atypical in a civilian environment, including IEDs, RPG attack, mortar rounds, and witnessing service member and civilian casualties. Military personnel may additionally be tasked with clean-up of combat aftermath, requiring service members to handle human remains. Other contextual factors that complicate presentation and assessment include the lack of opportunity to comply with recommended postconcussive care (e.g., rest) in a combat zone and the military cultural context, in which fear of stigma, professional repercussions, or cultural norms prevent persons from seeking treatment.

Although this book chapter focuses on service-related TBI, these injuries occur with service members who experience life events prior to, during, and after the event that led to the MTBI. Mental health comorbidities within service members and veterans—such as substance use, posttraumatic stress, depression, and anxiety—represent a complicating factor when describing service-related MTBI. The mental health of U.S. military personnel across eras has been extensively studied prior to, during, and following military service. Therefore, it is possible to account for

mental health-related factors that may contribute to outcomes following MTBI.

There are population-level mental health disparities between those who do and do not enter into military service. Excluding those who were drafted, U.S. adults who report a history of military service are more likely to report a history of adverse childhood experiences, such as sexual abuse and exposure to domestic violence.[30] Although all U.S. military branches utilize mental health screening for military recruits, retrospective report from one study indicated that 20% of active-duty army soldiers had a psychiatric disorder with onset prior to enlistment.[31] Exposure to the extreme psychological stress and physical demands associated with military service can modify baseline physiology at the time of injury and make it difficult to detect postconcussion symptoms, such as inattention, irritability, and sleep problems. This baseline alteration in physiology may also alter or amplify the actual biochemical events that occur in the acute stages of concussion. Clinical presentations that may affect symptoms following MTBI include comorbid injury, chronic pain, sleep disorders, substance use disorders, PTSD, and depression.

PTSD and MTBI

There are high rates of PTSD and depression symptomatology within service members and veterans presenting for clinical treatment following MTBI. Moreover, symptoms characteristic of MTBI (such as inattention or difficulty sleeping) can often be quite similar to PTSD and/or depression symptoms. Table 32.3 illustrates the overlap between postconcussive symptoms, PTSD symptoms, and depression symptoms. This overlap results in a complicated clinical picture in evaluating service members and veterans who may have current PTSD or depression symptoms as well as a history of MTBI.

Table 32.3 Overlap of symptoms between postconcussive and PTSD/depression

Postconcussion symptoms[a]	Overlaps with PTSD/depression
Headaches	
Dizziness/light-headedness	
Nausea/feeling sick	
Fatigue	X
Sensitivity to noise	X
Irritable	X
Sadness	X
Nervous or tense	X
Temper problems	X
Poor concentration	X
Memory problems	X
Difficulty reading	X
Poor sleep	X
Sensitivity to light[b]	
Change of taste/smell[b]	

[a] List of postconcussion symptoms from Iverson, Zasler, and Lange.[32] (p. 379)

[b] Also frequently listed as postconcussion symptoms.

The commonalities of PTSD and postconcussion symptoms are well illustrated in a study by Schneiderman et al.,[32] who surveyed 2,235 OEF/OIF military personnel, and found that 12% reported a history consistent with TBI, and 11% screened positive for PTSD. Higher rates of PTSD occurred in those reporting polytrauma and combat-related MTBI. Further, the best predictor of postconcussive symptoms was the presence of PTSD after the overlapping symptoms were extracted from PTSD scores. MTBI also appears to increase the severity of PTSD symptoms. To further examine the relationship between MTBI and PTSD symptoms in U.S. military, Hoge et al.[11] reported on 2,525 deployed soldiers who indicated deployment-related MTBI with or without LOC or altered mental status. Of soldiers who reported MTBI with LOC, 44% met criteria for PTSD versus 27% of those with altered mental status. This is also contrasted with soldiers who indicated no head injury during deployment, of whom only 9% met criteria for PTSD. The effect of MTBI on PTSD severity was investigated in a study by Yurgil et al.[33] which assessed 1,648 Marine and Navy service members prior to and following OEF/OIF deployment. They found that, independent of combat exposure, deployment-related MTBI was associated with a 23% increase in PTSD severity. These findings overall indicate the importance for PTSD screening in service members and veterans with known MTBI history.

Although cognitive problems are often reported by service members and veterans with MTBI history, they are not specific to MTBI. In a prospective cohort-controlled study by Vasterling et al.,[34] active-duty Army soldiers (n = 654) were compared to nondeployed soldiers (n = 307) prior to and after deployment to OIF on mood and neuropsychological measures. Not surprisingly, deployed soldiers demonstrated compromise in sustained attention, verbal learning and memory, and visual–spatial memory. In addition, those who were deployed reported increased negative state affect for confusion and tension. An interesting additional finding was the fact that, after controlling for deployment-related TBI, stress, and depression symptoms, these cognitive and mood findings held. These findings point to the presence of cognitive performance decrements secondary to deployment even without the presence of known TBI.

There is now further evidence that persistent cognitive symptoms in service members and veterans with PTSD and a history of MTBI are most likely driven by psychiatric symptomatology. A study by Shandera-Ochsner et al.[35] investigated neurocognitive group differences between OEF/OIF/OND combat veterans with MTBI, PTSD, both, or neither in order to clarify the independent contributions of MTBI and PTSD to detriments in cognitive performance. Veterans with comorbid combat-related PTSD and MTBI as well as those with PTSD only showed decreased performance in verbal fluency, verbal memory, and executive

function whereas those with MTBI only did not exhibit such differences. This indicates that in service members with a history of MTBI, there are often significant mental health contributions to persistent cognitive symptoms. Because there is considerable overlap between symptoms associated with PTSD and postconcussive symptoms, it is important to conduct a thorough assessment to ensure that the appropriate etiologies are identified.

MTBI and other mental health concerns

Several other comorbid psychiatric concerns are prevalent among service members and veterans who experience MTBI, including primary sleep disorders, depression, substance use disorders, and self-directed violence. As mentioned previously, many service members enter the military with existing mental health concerns, such as intermittent explosive disorder, attention deficit hyperactivity disorder, and PTSD.[31] Regardless of a service member's preenlistment mental health, military service is associated with lifestyle changes, chronic stressors, and traumatic exposures that can increase risk for psychiatric disorders. In a longitudinal assessment of mental health symptoms, 88,235 soldiers completed Post Deployment Health Assessment (PDHA) and PDHRA (reassessment) at least 6 months apart.[36] The authors found that rates of any mental health concerns increased from approximately 18% to 29% in the first 6 months postdeployment among active-duty soldiers and from 16% to 38% among those from the Reserves or National Guard. In addition to mental health concerns that arise during deployment, many individuals find that following military separation, psychological symptoms may persist or even worsen. This section explores mental health concerns beyond PTSD that may affect functioning following MTBI.

DEPRESSION

Although much attention has been focused on the overlap in symptoms between PTSD and MTBI, depression also represents a major contributing factor to postconcussive symptoms. Several key physiological and cognitive symptoms and features of depression may affect postconcussive functioning, including fatigue, sleep problems, poor concentration, psychomotor slowing, and low mood. Wilk et al.[37] found that among Army service members returning from OEF/OIF deployment in 2008, 23% of those who sustained MTBI with LOC screened positive for depression. In that study, both depression and PTSD better accounted for many postconcussive symptoms than history of MTBI. Notably, depression predicted risk of headache pain as strongly as multiple MTBI history. Furthermore, depression and PTSD are both more strongly linked to cognitive problems than history of MTBI.[38] Given the physiological and cognitive problems associated with depression, evaluation following MTBI should include in-depth assessment of history of past depressive episodes as well as current symptoms.

SUBSTANCE USE

Historically and currently, there are high rates of heavy alcohol consumption in the military, with 20% of active-duty service members endorsing binge drinking in the past month.[39] Veteran populations similarly drink heavily compared to those who never served in the military.[40] Although there is not consistent evidence of an increase in drinking following MTBI, alcohol use should be assessed among individuals with a history of MTBI. A study by Heltemes et al.[41] found that among 1,413 service members treated for MTBI in OEF/OIF combat zones from 2004 to 2007, 6% were later diagnosed with postdeployment alcohol use disorders prior to military separation. During U.S. Air Force service, 15% of airmen diagnosed with MTBI are also clinically diagnosed with an alcohol use disorder.[42] Among veterans, rates of alcohol use among those receiving MTBI evaluation may be higher with up to 35% screening positive for alcohol use disorder.[43] Given that cognitive symptoms are common among those with heavy substance use, service members and veterans presenting with persistent postconcussive symptoms should be screened for alcohol use and other substance use disorders.

SLEEP PROBLEMS

Disordered sleep is common among postconcussive symptoms and may arise among veterans presenting with a variety of physical and mental health concerns. Although many etiologies of sleep disorder may be physiological, behavioral interventions often present a viable means of improving sleep quality and duration.[44]

SELF-DIRECTED VIOLENCE

Increasingly, attention within DoD and VHA has shifted to generating strategies for preventing service member and veteran suicide. Some research has indicated increased risk for suicidal ideation and death by suicide among those with a history of MTBI,[45,46] and other evidence suggests that the relationship between MTBI and suicide risk factors is mediated by psychiatric comorbidities, such as PTSD.[47] Regardless of the mechanisms of suicide risk within MTBI, it is imperative for clinicians to proactively assess for suicidal ideation and take steps to minimize suicide risk. This may include completing a safety plan, removing means, contacting family members, and treating underlying psychological symptoms driving suicidal ideation.

COMMON CONDITIONS OF POLYTRAUMA

As noted earlier in this book chapter, Owens et al.[14] reported on the data gathered through the Joint Theater Trauma Registry (JTTR) in which 6,609 combat wounds were recorded among 1,566 combatants. The largest percentage of these wounds were extremity injuries (54%), followed by abdomen (11%), and face wounds (10%). Other wounds were distributed among head, eyes, ears, neck, and thorax. This

particular profile of extremity wounds is highly likely secondary to the protection offered by body armor around vital body organs but leaving the extremities exposed. Extremity injuries occurred in similar proportions in the WWII, Korea, and Vietnam war conflicts. Wade et al.[48] reported on the U.S. Navy-Marine Corps Combat Trauma Registry data in a retrospective analysis of the period covered by March 1, 2004, to September 30, 2004, in OIF. The focus of this data review was on head, face, and neck injuries (HFNIs), and the majority of these were face injuries (65%), again largely attributable to IED explosions. They note that, despite the protection to penetrating head and chest injuries with modern Kevlar body armor, the face is exposed to injury.

Polytrauma injuries are characterized by significant problems with chronic musculoskeletal pain, persistent headaches, vision and hearing loss, traumatic amputations, and other problems that are consistent with the above injury reporting data. Since fiscal year 2002 (FY2002), the Veterans Health Administration Office of Public Health reports health care utilization data[49] that includes the numbers of veterans in OEF/OIF/OND that have enrolled for VA care with descriptive statistics on the distribution of diagnoses and conditions that appear in the VHA administrative database. The reader is directed to this website for the most recent data available. According to data up to the third fiscal quarter of 2014 (September), there were close to 1.1 million veterans enrolled for VHA care since FY2002, which represents approximately 60% of those who separated from military service. Please note that military service members are not required to enroll for VHA care, and the percentage of those who have enrolled after separation has increased over the past decade. Of the 1.1 million, 61% were former active-duty service members, and 59% were from the Reserve/National Guard component of service. In rank order, the top five disease diagnoses (per ICD-9-CM categories) were 1) diseases of the musculoskeletal system (ICD-9-CM codes 710–739, 60.5%); 2) mental disorders (290–319, 56.5%); 3) symptoms, signs, and ill-defined conditions (780–799, 56.4%); 4) diseases of the nervous system/sense organs (280–289, 49.3%); and 5) diseases of the digestive system (520–579, 37.3%). The rankings of the top three of these categories has remained stable and in the same order since FY2002. The top two mental health diagnoses in the VHA database were 1) PTSD (n = 337,285 out of 1.1 million) and 2) depressive disorders (n = 270,005).

Other conditions that are commonly seen in VA health care are worthy of mention as there appears to be a common cluster of symptoms, particularly those seen in both mental health service lines and in polytrauma rehabilitation settings. *Chronic pain* is prevalent among OEF/OIF veterans as reported in a sample of veterans seeking treatment at a VA Medical Center by Gironda et al.[50] In this sample, 28% (n = 219 out of a total 793 whose charts included pain documentation) reported moderate-to-severe pain intensity. Common diagnoses in this cohort were musculoskeletal and connective tissue disorders for 82% of those whose pain duration was greater than 1 month. Among those with TBI, *headaches* were common in this group of OEF/OIF veterans with polytrauma. A good example of the multiple co-occurring conditions for which the presence of chronic headaches are frequent are findings published by Ruff et al.[51] who found that, out of 126 veterans who screened positive on the aforementioned TBI screens, 80 demonstrated neurological impairment. Those with impairment had a history of multiple blast exposures, higher frequency of headaches (including migraine), more severe chronic pain, PTSD, and sleep disturbances with nightmares. *Migraines* have also been found to be prevalent in U.S. Army soldiers who returned from a 1-year deployment to Iraq.[52] Among this group, 19% were found to screen positive for migraine headaches with another 17% noted to have possible migraines.

Military operations involve the use of an array of weaponry, and war environments are characterized by exposure to explosives and other events (e.g., open fire pits) that can lead to *burns*. Patients in OEF/OIF with burns are treated at the U.S. Army Institute of Surgical Research in San Antonio, Texas. During the inclusion period of April 2003 to April 2005, it was found that 55% of burns were caused by IED blasts, followed by 16% due to VBIED, 15% due to RPG, 7% secondary to mortar round exposure, and 4% due to landmine exposure.[53] Of those casualties, hand and head areas of the body comprised the greatest percentage (80% and 77%, respectively). Burn mechanisms in the deployed setting occur as a direct result of heat from the explosive blast and from the secondary effect of burning vehicles, clothing, and equipment.

Ocular trauma and perforating globe injuries also occur as a result of blast exposures. Because the eyes are fluid-filled organs, they are vulnerable to damage secondary to the primary overpressurization wave (both positive and negative phases of the blast wind cycle) and to fragment injuries that result from the explosive device and secondary damage.[54–56]

Dizziness, *balance*, and *vestibular disorders* occur as a consequence of TBI, and these are also seen after blast exposures. The primary blast overpressurization wave can cause tympanic membrane damage and rupture, and damage to the inner ear canals occurs. In mild TBI, dizziness problems can occur as well,[57] and dizziness problems can be complicated by musculoskeletal injuries acquired in theater.

Traumatic amputations are another consequence of blast wave exposures and other events that occur in the deployed setting. In terms of blast-related injury, the majority of explosions tend to occur from ground-implanted IEDs with which lower extremity amputations are more common. In a retrospective analysis of 8,058 military casualties in Iraq and Afghanistan between October 2001 and June 2006, 70.5% of these were listed as having a major limb injury. Of those having had a major limb injury, 7.4% underwent a limb amputation.[58] This is compared to an 8.3% rate of limb amputation during the Vietnam War among those with major limb injury. These rates were judged to be comparable. Facing those who are postamputees of the OEF and OIF conflicts are potential problems with skin breakdown and subsequent surgery, phantom limb pain problems, and

possibility of heterotopic ossification (HO). Regarding HO, Potter et al.[59] found that HO was identified in 134 (63%) of the 213 residual limbs among a group of 330 patients from OEF/OIF with a total of 373 traumatic and combat-related amputations.

ASSESSMENT OF CO-OCCURRING DISORDERS

A key issue to assist with accurate diagnosis of PTSD symptomatology in those who have experienced blast injury is to include several well-validated instruments that are available to evaluate PTSD symptoms, and these are recommended for use in conjunction with a clinical interview. A version of the PTSD Checklist (PCL) that is specific to military experiences (PCL-M) has been developed and validated for this purpose.

More information about brief screening instruments is available at the National PTSD website (http://www.ncptsd.va.gov) as are numerous other resources that are available to the public, veterans, family members, health care providers, and researchers from that website. Similarly, there are multiple inventories available to evaluate for symptoms of depressive disorders, including the Patient Health Questionnaire–9, which is a 9-item self-report module from the Primary Care Evaluation of Mental Disorders (PRIME-MD)[38] that assesses depressive symptom severity and screens for major and minor depressive episodes.

Assessment of combat-related stress is important for returning service members. These measures allow the clinician to understand the breadth and depth of experiences that may be unique to war zone deployment. Further, it helps to define the types of traumatic exposures that may be playing a role in initiating and maintaining mental health problems that arise out of war. It is important that, when assessing the active-duty service member or veteran, what may appear to be the most traumatic event to the clinician may not necessarily be the most traumatic to the service member. Therefore, self-report questionnaires may be seen as a beginning point to understanding the types and nature of traumatic events that may be fueling PTSD symptoms and prolonging functional disability in these individuals. One such instrument, the Combat Experiences Scale (an 18-item dichotomous "yes" and "no" response inventory) lists items/experiences such as "While deployed, I went on combat patrols or missions;" "While deployed, I or members of my unit were attacked by terrorists or civilians;" "While deployed, my unit engaged in battle in which it suffered casualties." These items will assess not only the array of combat stressors, but will also denote the level of combat intensity which, in previous studies cited in this chapter, has been associated with the presence of PTSD.

Within VHA Medical Centers and VA Community Based Outpatient Centers (CBOCs), processes are in place to provide mandatory screening for PTSD, Iraq/Afghanistan exposure screening, and TBI screening once a service member separates from the military and becomes a veteran. Throughout each service line with the VHA, clinicians are alerted to these templates and interactive screening procedures via the electronic medical chart. Notices show on the electronic chart regarding which screens are due, and clinicians from any discipline who see the veteran within the medical center or CBOC (including primary care physicians, psychologists, mental health clinicians, dentists, nursing staff, and others) have been trained to ask specific questions that, if the screen is positive, initiates further evaluations for conditions of PTSD, suicidality, depression, alcohol abuse, and TBI. These simple screening questions are meant to more easily assess and more systematically engage the veteran in a process of comprehensive postcombat care evaluations in order to develop effective plans of care.

Positive responses to screening measures with VHA health care triggers mandatory action for follow-up. For example, a positive TBI screen will trigger a comprehensive TBI evaluation conducted by a physical medicine and rehabilitation physician or neurologist. Often, this evaluation is completed within the context of a polytrauma rehabilitation program in which rehabilitation psychologists, neuropsychologists, other mental health personnel, and social work/case managers along with physical, occupational, speech, and recreation therapists also see the patient for evaluation and rehabilitation. Hence, the Polytrauma System of Care was set up to provide a rehabilitation setting within which multiple co-occurring conditions can be treated. Much is also being done to integrate primary care and mental health in VHA called Primary Care Mental Health Integration (PCMHI) services within VHA to provide collaborative care with an emphasis upon reducing fragmentation of services. Assessment of co-occurring conditions can also be initiated within PCMHI services, where the service member or veteran may be then referred for specialty services, such as those provided by a polytrauma program.

POLYTRAUMA REHABILITATION AND INTEGRATED CARE APPROACHES

The system of care for TBI and polytrauma is meant to extend from the deployed setting through care delivered in VHA facilities and in the community. For the conflicts of OEF/OIF/OND, efforts toward coordinating DoD and Department of Veterans Affairs health care have been unprecedented. Efforts toward visibility of electronic health records generated in the DoD by VHA providers are now being implemented (via the Joint Legacy Viewer initiative), which contributes to a more smooth transition between these health care systems. All VA health care facilities utilize the same electronic health record across the VHA system for both inpatient and outpatient encounters. Active-duty service members can be seen at all VA Medical Centers because the latter are all within the tricare provider network. Military medical centers can be easily located through the Tricare website (http://www.tricare.mil/mtf/), and VA facilities can also be located through a directory

search via the VHA website (http://www.va.gov/directory/guide/division_flsh.asp?dnum=1).

VHA polytrauma system of care

In 2005, the VHA issued a directive to create the Polytrauma System of Care. In place, up to that time, were the existing Defense and Veterans' Brain Injury Centers (established in 1992 as the Defense and Veterans' Head Injury Program) with locations at the WRAMC, Naval Medical Center San Diego, and Brooke Army Medical Center/Wilford Hall Medical Center (San Antonio, Texas) as well as the VA Medical Centers located in Tampa, Florida; Minneapolis, Minnesota; Richmond, Virginia; and Palo Alto, California. As of 2015, the VHA Polytrauma System of Care (see the following website for details: http://www.polytrauma.va.gov/) is a four-tier integrated care network consisting of five Polytrauma Rehabilitation Centers (PRCs), which are embedded within the five VA Medical Centers located in Tampa, Minneapolis, Richmond, Palo Alto, and San Antonio; 23 Polytrauma Network Site Programs (PNS) (one per each VHA region known as a Vicinity Integrated Service Network); and 87 Polytrauma Support Clinic Teams (PSCTs), which are located at smaller and more local VA Medical Centers. There are 39 Polytrauma Points of Contact (PPOCs) at VA Medical Centers without specialized rehabilitation programs. The PPOCs are designated to connect patients with the Polytrauma System of Care and other local resources. This large system of care was put into place in a relatively short period of time and provides a full range of acute, transitional living, postacute, and community/vocational reentry rehabilitation services for OEF/OIF veterans and active-duty service members. Some components of care for those with MTBI and polytrauma are listed below.

ACUTE CARE OF CONCUSSION

Evaluation and management of the consequences of concussion are often difficult to initiate in the deployed environment. However, new policies for in-theater management of concussion has been successfully implemented. The DoD issued what is called a DoD Instruction (DoDI) in September 2012 titled "DoD Policy Guidance for Management of Mild Traumatic Brain Injury/Concussion in the Deployed Setting." The policy requires the tracking of concussive events in service members, and implementation of clinical practice guidelines for the management of concussion in the deployed setting. The policy defines the necessity of medical evaluation as close to the concussive event as is possible in the deployed setting, a reporting structure for these events, and implementation of clinical guidance as has been described by the Defense Center of Excellence for Psychological Health and Traumatic Brain Injury (see http://www.dcoe.mil/About_DCoE.aspx). The DoDI also provides guidance regarding multiple concussion management. A neurologist or other qualified health care provider determines return-to-duty status. A brief period of rest followed by gradual resumption of activities is frequently recommended and implemented, consistent with what is often found in sports concussion return-to-play recommendations. See Silverberg and Iverson[60] for further details of the history and recommendations regarding activity resumption after concussion.

In general, acute management of concussion is guided by the accumulated wisdom from the sports concussion literature. After a Grade I concussion, a service member should be examined immediately and subsequently monitored every 5 minutes for 15 minutes to ensure that mental status abnormalities or postconcussive symptoms clear within 15 minutes. If this is the case, they may resume duties usually after medical evaluation. After a Grade II concussion, it is recommended that the service member be immediately removed from the situation, allowed to rest, and examined frequently for 24 to 48 hours for signs of evolving intracranial pathology and cleared by a physician or other qualified medical provider before resuming duties after a full asymptomatic rest and with exertion. After a Grade III concussion, the service member should be emergently treated. Treatment should include a thorough neurological evaluation, if available and indicated. Further evaluation and possible transport to a combat medical setting is indicated if any signs of pathology are detected or if the mental status of the service member remains abnormal.

POSTACUTE CARE FOR MTBI

For those who have been injured within the past 3 months, the primary treatment is education about expected symptoms, course of recovery, strategies to ensure adequate rest, gradual resumption of normal level of activities, and signs and symptoms to watch that might indicate additional evaluation or treatment is needed. A brief cognitive–behavioral intervention developed by Ferguson and Mittenberg[61] has been useful to prevent or minimize the longer-term impact or persistence of postconcussive symptomatology.

TREATMENT BEYOND 6 MONTHS

By definition, if a patient is seeking treatment for MTBI beyond 6 months, they are seeking treatment for postconcussion syndrome. The principal tenet of treatment at this stage is symptom-specific. The clinician is advised to treat the primary condition(s) (i.e., those that explain most or all of the symptoms). For example, complaints of ongoing memory or attentional difficulties would warrant consideration of neuropsychological assessment and cognitive rehabilitation therapies as indicated. Complaints of mood symptoms (irritability, depression, or anxious mood) would warrant psychologically, behaviorally, or pharmacologically oriented therapies. The presence of a significant comorbid psychiatric condition, such as PTSD or alcohol abuse, would also be a primary focus of intervention as this would be

expected to have impact for functional improvement. Each of these is discussed in detail here.

TREATMENT OF COGNITIVE SEQUELAE IN POLYTRAUMA

Those who are seen for polytrauma rehabilitation frequently present with cognitive complaints. Such cognitive problems are likely a result of a combination of conditions, including the aftereffects of multiple concussions and presence of PTSD, chronic pain, and sleep disorders. The cognitive problems presented by the patient with blast-related TBI are not significantly different from those TBIs that are due to nonblast mechanisms, such as motor vehicle accidents, falls, or other blunt head trauma.[62] The study also found a higher rate of PTSD among those with blast-related TBI, again underscoring the complex clinical presentations of this population. If cognitive impairments are identified through a comprehensive polytrauma team evaluation, then engagement of a rehabilitation team, particularly speech–language pathology, occupational therapy, neuropsychology, and vocational rehabilitation might be indicated with a focus on developing compensatory cognitive strategies and symptoms. Additionally, the rehabilitation team can provide TBI education and support to both the patient and his or her family. Appropriate treatment can be delivered in individual or group format. Considerable literature exists supporting the efficacy of group-based therapy for individuals who are status post-MTBI.[63,64] Sample components of group-based cognitive rehabilitation are listed subsequently.

A group designed to enhance compensatory cognitive skills after MTBI should address several core components, including attention, memory, and executive function. Sohlberg and Mateer's[65] "Clinical Model of Attention" is recommended as a foundation for improving attention. Based on this model, the clinician would focus on the development of strategies and environmental supports to change the type of attention required, such as reducing distractions (thus, moving from selective attention to sustained or focused attention), breaking tasks into smaller chunks (thus, moving from sustained to focused attention), prioritizing and simplifying tasks (thus, moving from tasks that require divided or alternating attention to focused or sustained attention), and using external aids (e.g., checklists; alarms; electronic organizers; task-specific devices, such as key hooks; pill box reminders). Several prospective trials have indicated that such strategies are effective in improving day-to-day attentional abilities.[66,67] Group participants should be encouraged to concurrently enlist psychosocial support as an adjunct to all attention strategies and become educated about the ways that non-neurocognitive factors (e.g., sleep deprivation, pain, psychological distress) can detract from attentional abilities. To evaluate the effectiveness of such strategies, ongoing self-evaluation in daily function is indicated rather than formal neuropsychological testing.

To address memory concerns post-TBI, a group should include the development of prospective memory strategies and systems with emphasis on the selection and refinement of compensatory memory tools. Several prospective studies have indicated that such strategies are effective for persons with MTBI-related impairments. Cotreatment with speech–language pathology and psychology is often helpful to develop these strategies. High-tech tools to aid memory (e.g., digital voice recorders; smartphones; use of apps on tablets, computers, and other personal electronic devices) are appealing to the military cohort and have been shown to be effective strategies for aiding prospective memory.[68,69] Development of memory systems needs to be highly tailored to each individual within the class and conceptualized as an ongoing "work in progress."

MANAGING MOOD AFTER TBI

Among the most prevalent mental health concerns that affect participants' abilities to effectively utilize compensatory cognitive strategies after TBI are depression,[70] anxiety, irritability, impulsivity, lability, lack of insight, and problematic substance use.[71] Mental health treatment can address these affective and behavioral dysregulation problems through education, social support, improved deficit awareness, and development of self-monitoring and problem-solving skills. By addressing underlying mental health concerns, the participant may find that compensatory cognitive strategies are more accessible and feasible. Some practical aspects of leading group psychotherapy for MTBI are summarized in Delmonico, Hanley-Peterson, and Englander.[72]

Within the VHA, veterans with MTBI history may have access to a variety of evidence-based psychotherapies (EBPs) to treat co-occurring psychiatric disorders. In the largest roll-out to date within VHA of EBPs, VA treatment facilities across the United States have provided training and supervision to mental health providers in two PTSD treatments (cognitive processing therapy and prolonged exposure therapy) and three depression treatments (cognitive behavioral therapy, acceptance and commitment therapy, and interpersonal therapy). VHA policy now states that these treatments must be available and offered to veterans with PTSD or depression.[73] Other EBPs recognized by the VHA for treatment of individual mental health concerns that may be relevant to MTBI include the following: cognitive behavioral therapy (CBT) for insomnia, CBT for pain management, motivational interviewing, motivational enhancement therapy, and CBT for substance use disorders.

FAMILY SUPPORT

For active-duty service members, deployment alone carries with it separation from family members and the stress associated with that separation. In the case of service members with serious injuries, family members frequently assume the burdens of physically caring for their injured family member and advocating for their family member as well as assuming increased financial, parenting, and house management duties. When injuries include brain injury, mental illness, or other conditions that affect the service members'

cognitive and psychological function, relationships may evidence strain in the realms of intimacy and relationship satisfaction, secondary traumatization may occur, and increased rates of aggression and intimate-partner violence have been reported. Caregivers are at significant risk for increased health and mood problems of their own. When these problems are superimposed upon the existing stresses related to deployment, families are particularly vulnerable and in need of support.

Within the military, formal support programs for families have increasingly been put into place. In 2011, a White House Report titled "Strengthening Our Military Families: Meeting America's Commitment" accompanied U.S. government-wide efforts to increase support for military families. These efforts have included programming and support from DoD, VHA, the Department of Health and Human Services, the Department of Agriculture, and the Department of Labor, among others. Within the VHA, families and partners can be supported through EBPs for couples therapy as well as increasing availability of parent training and family education regarding MTBI and co-occurring disorders.

IMPORTANCE AND POTENTIAL ROLE OF PEER SUPPORT AND VISITATION

Since the time of the Vietnam War, the importance of peer support for and by veterans has been critical among approaches to assist veterans with combat-related injuries. The inception and success of the Vet Centers around the United States attests to the need for both professional and peer support for PTSD as an example. In the polytrauma population, peer visitation (PV) can provide individuals coping with multiple disorders and disability an opportunity to interact with a peer who has survived and managed a similar condition. The effectiveness of PV is well explained by social learning theory[74]; through observation of successful role models, we increase self-efficacy and learn specific actions and coping strategies. Such increases in efficacy and knowledge can, in turn, engender hope and improve motivation to engage in treatment.

In current practice, peer support is provided in group or one-on-one settings, face-to-face or virtual settings, may or may not involve training for the peer leader, and may or may not be overseen by an organization or allied health professional.[75] Many PV programs are tailored for persons with medical conditions. Some organizations offer nationally based PV programs (e.g., the National Spinal Cord Injury Association and the Amputee Coalition of America), and others operate more regionally.[76–79] Although many organizations offer PV, there is great inconsistency in their provision of training, methods of matching of visitors to recipients, and evaluating visits.

In spite of the widespread availability of PV programs, empirical support for their efficacy is limited. Of the limited literature available, most is comprised of retrospective qualitative evaluations of peer visits. This literature consistently indicates that recipients find peer support beneficial.[79–82] For example, in one study of a PV program for persons with spinal cord injury, recipients of a PV reported that they perceived PVs as providing a unique type of social support that was more credible, provided more practical and detailed information than is given by clinicians, inspired hope, and relieved distress.[83] In a study of women newly diagnosed with breast cancer and participating in a cancer support service, 53% reported that meeting someone with a similar experience was the most important aspect of the program, and 89% said that they would definitely recommend this to others.[84]

The handful of studies that have examined more objective outcomes indicate that continued efforts to develop and evaluate PV are warranted. In one of the few case-control studies published, breast cancer patients who received peer mentorship through the Canadian Cancer Society's "Reach to Recovery" program reported decreased feelings of isolation, increased optimism for the future, increased knowledge of treatment and coping options, increased coping ability, and improved functional social support and relationships with their doctors compared to case controls who did not have PV.[85] Participants in this program identified peer knowledge as a key aspect of PV; participants were 11 times more likely to report satisfaction with the program if they felt their peer visitor was helpful in answering their questions. Other important aspects of PV that have been identified across studies are good PV listening skills,[75] perceived similarity between visitor and patient,[76] and perceived supportiveness of the peer visitor.[81] These latter findings underscore the importance of screening and training peer visitors appropriately. Despite growing program availability and encouraging empirical support, peer support programs are used by a minority (20%–30%) of those who might benefit.[80]

Apropos to OEF/OIF active-duty service members and veterans with polytrauma, application of peer support approaches is found in the Traumatic Brain Injury Model System of Care in Santa Clara, California, which includes a peer support component.[86] Both peer visitors and recipients of PV can be either individuals who have survived an injury or a family member of a person who has survived a brain injury. Although the program has not been empirically evaluated, qualitative data indicate that it is not only possible but ultimately therapeutic for persons with brain injury to provide peer support to more recently injured persons (once they have achieved a significant degree of recovery themselves). The authors support the importance of a thorough initial training as well as ongoing education and programmatic support.

CONCLUSIONS

Each war conflict tends to be characterized by specific types of injuries, and as a consequence, new medical innovations and health care delivery models emerge. Evolving from the concept of "shell shock" and associated "war neuroses," we are now applying modern scientific knowledge regarding MTBI, evidence-based treatments for PTSD, and new models of

rehabilitation for deployment- and nondeployment-related injuries, such as the VHA Polytrauma System of Care to active-duty service members and veterans. Greater awareness of the medical, psychological, and rehabilitation needs by health care providers at military treatment facilities, VHA care systems, and community providers has advanced the efficacy and efficiency to those who have experienced blast-related TBI and polytrauma. As this system of care evolves, a better understanding of the complex set of problems that are presented by OEF/OIF/OND service members and veterans will emerge despite some of the current controversies that continue to arise with regard to the nature of the disorders presented by this population.[87] Delivering services to those with combat-related injuries with polytrauma and developing understanding of the needs and effective interventions for family members[88,89] and caregivers will likely characterize future efforts at VHA facilities.

Advances in the rehabilitation of individuals with TBI are being realized along with emerging and evidence-based approaches developed in the application of exercise, pharmacological intervention, and other therapeutic treatments.[90] A clearer understanding of the role of neurorehabilitation strategies is emerging for deployment-related TBI. In a recent multicenter randomized controlled trial conducted by Vanderploeg et al.,[91] cognitive–didactic versus functional–experiential rehabilitation approaches were compared in active-duty service members with TBI. Long-term functional outcomes (independence in living skills, work/school reentry) were similar in both approaches whereas the cognitive–didactic group fared better with regard to posttreatment cognitive functioning. Further work will be needed to develop specific and efficacious neurorehabilitation strategies, of both compensatory and restorative nature, to address the continuing and growing needs of active-duty service members and veterans who sustained blast injuries and subsequent polytrauma.

Conceptualizing service member and veteran TBI and polytrauma from a holistic standpoint, in our experience, has been critical in guiding rehabilitation interventions. We have argued that the convergence of multiple traumas and conditions that service members can experience led to a complicated situation of co-occurring disorders when first presenting to VA health care.[92] Often, veterans of OEF/OIF/OND suffer from a host of converging conditions that produce a profile of symptoms, many of which cannot be directly tied to one diagnosis versus another. For example, symptoms of cognitive impairment may not necessarily be a marker for the presence of that person having experienced a TBI. It may, in fact, be a result of several candidate contributors: chronic pain with opioid analgesia, sleep dysfunction and/or obstructive sleep apnea, PTSD, and depression. Rather, the combination of candidate contributors forms a final common pathway of postdeployment conditions that create difficulties in daily activities and decreased participation in meaningful life activities (e.g., college course work, competitive employment, family life, friendship network, engagement in community activities). The postdeployment condition, as described here, clearly is not restricted to those who have served in OEF/OIF/OND and extends to all war era veterans. As earlier war veteran cohorts age, these postdeployment conditions interact with other medical problems due to aging (e.g., vascular risks, mild cognitive impairment/dementia, chronic illness). A model of holistic rehabilitation that integrates the care of veterans is, therefore, critical across the life span of the veteran.

Finally, it should be said that effective delivery of care to military personnel and veterans will rely on the ability of the larger organizations and systems of care that are brought to bear to care for these individuals. The interdisciplinary rehabilitation team is the lowest common denominator in polytrauma care, and formulating interventions requires a philosophy of postcombat care that appreciates the significant synthesis of psychological, physical,[93] and existential dimensions of coping and suffering, the latter defined by Cassel[94] as "a specific state of distress that occurs when the intactness or integrity of the person is threatened or disrupted." (p. 531) An integrated care approach requires the collaboration of postcombat care and polytrauma rehabilitation teams. Their success in promoting resilience and coping, improving functioning, and facilitating community reintegration such that the "threat to the integrity of the person" is diminished or eliminated will hinge also on partnerships of teams with their surrounding organization and the organization's ability to support and collaborate with postcombat care teams. To this point, Strasser, Uomoto, and Smits[95] state the following:

> Our "prescription for partnership" represents a progression to a cellular level of the organization, namely, the interdisciplinary team. This partnership needs to be an interactive process in which insights gained at the level of the team integrate with other service providers, senior leadership, and stakeholders in other key organizations… We owe it to our patients and our future patients to critically examine the underpinnings of the rehabilitation process and to incorporate the knowledge gained into new practice strategies and approaches. (p. 180)

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Issues in aging following traumatic brain injury

GRACE S. GRIESBACH, MARK J. ASHLEY, AND ALAN WEINTRAUB*

INTRODUCTION

There is a rapidly growing population of more than 5.3 million persons living with traumatic brain injury (TBI) in the United States.[1] As discussed in other chapters, TBI can result in multiple functional deficits leading to disability. Unfortunately, the effects of TBI become more evident as aging takes place. As the TBI population ages, survivors, practitioners, caregivers, and financially responsible parties alike must consider the neuromedical issues associated with aging and TBI. These parties must attempt to anticipate the issues to be faced by this population and further attempt to put in place mechanisms that might address those problems. Here, we describe the long-term consequences of TBI. We indicate the impact that TBI has on later life within the occupational, social, and financial realms. There is a notable interplay between TBI and age-related changes. Given this, we, then proceed with describing long-term neurological effects of TBI and how these can impact diseases associated with aging. It is important to keep in consideration that the trajectory of recovery is dependent upon when TBI is sustained. A TBI sustained earlier in adult life is likely to have an influence on normal aging processes over time and should be distinguished from suffering a TBI at an advanced age. Finally, we pinpoint factors that may facilitate the prognosis of TBI. In addition to providing valuable information for clinical studies, identification of these factors can facilitate potential interventions to alleviate the negative effects of TBI over time.

* Previous Contributor.

CONSEQUENCES OF AGING WITH A TBI

Occupational and social consequences

The economic and social impact of TBI within the United States is noteworthy. It is estimated that 5.3 million people in the United States are living with disabilities due to a TBI.[1] Prevalence is estimated at around 3.1 million individuals in the United States with incidence reported at 90 per 100,000.[2] Thurman et al.[3] estimate that between 80,000 and 90,000 persons per year become disabled as a result of TBI.

It is estimated that 20% of hospitalized survivors of TBI do not return to work due to injury-related disability. The total lifetime productivity costs have been estimated at $51.2 billion in 2000.[4] As such, TBI presents a major public health concern, both as a diagnosis in itself and, in particular, as the effects of aging are applied.[1] Returning to work is a major goal when treating TBI patients. An occupation not only provides financial benefits for the patient but also has a significant influence on quality of life.

Return to work is positively correlated to injury severity and usually estimated to range between 12% and 70% among TBI patients.[5] Meta-analysis of different studies confirms this link by showing that studies that include moderate and severe TBI patients are more likely to indicate a poor long-term occupational outcome.[6,7] In contrast, studies with mild

TBI (MTBI) subjects are more likely to show inconclusive findings.[7] Variability in work reentry is also observed when comparing different types of injury. For example, a large 15-year follow up study in a Vietnam veteran population with penetrating TBI showed that 82% of uninjured controls were working compared to 56% of TBI veterans.[8] In civilian populations, patients with penetrating TBI were less likely (49%) to be employed when compared to hospitalized controls (63%).[9] It should be noted that the occupational rates in the veteran group tended to be higher compared to civilian rates. This difference may be attributed to milder injuries in the veteran group as these principally included penetrating injuries involving shrapnel and, thus, tended to be more localized.[10]

There also appears to be an interaction between the age at which injury was sustained and the severity of the injury. It seems logical to assume that TBI inflicted upon a chronologically older brain would yield more disability and, consequently, more unemployment when compared to a similar injury sustained at a younger age.[11–13] Although this seems to hold true for cases of severe injury,[14,15] there is less support for injuries of lesser severity. For example, a prospective study by Rapoport and Feinstein found an inverse relationship associated with age and MTBI.[16] Older subjects (60+ years) fared better than their younger counterparts (18–59 years). Specifically, the older adults had higher Glasgow Outcome Scale scores, less physical symptomatology, less psychosocial impairment, and less psychological distress. A reason for these surprisingly better outcomes in an elderly MTBI population raises relevant theoretical considerations. Although the younger brain has clear biological advantages for recovery of function, the older person usually will have well-established "real-life" knowledge, structures, and routines in their day-to-day experience that may give them an advantage to facilitate a better functional outcome. Additionally, environmental demands associated with older adult lifestyles are often diminished in comparison to the demands placed upon younger adults.

As exemplified here, it is likely that employment rates are influenced by numerous extrinsic factors. One of these factors is exposure to rehabilitation. A systematic review of randomized controlled trials observed that the greatest benefits facilitating return to work were observed in those TBI patients that received postacute rehabilitation.[17] It should be noted that moderate-to-severe injuries are likely to show stronger rehabilitation benefits compared to MTBI given the degree of functional deficits.[18] An additional extrinsic factor that is likely to play a significant role in work reentry after TBI is the level of education. A 15-year follow-up study of Vietnam veterans indicated that those with more years of education were more likely to be employed after TBI.[19]

Age-related changes in sensory modalities, attention and perceptual reaction times are also likely to have an impact on occupational status. This is clearly illustrated in the case of driving. It is well accepted that driving skills may be negatively affected by aging.[20,21] Declining driving abilities are likely to be exacerbated when compounded with a TBI.[22] The ability to drive plays a critical role in social and occupational reintegration. Whereas this ability is affected by TBI in the average adult,[23] it is more so when TBI occurs at an advanced age. A TBI follow-up study indicates the probability of returning to drive decreases with age.[24]

Consideration of multiple factors should be acknowledged when interpreting long-term studies. This is illustrated in a large retrospective study involving occupational records of British soldiers injured in 1994.[25] This study found that return to work rates were dependent on age. Those soldiers that sustained a TBI at a younger age were more likely to continue in service compared to soldiers that endured a TBI at an older age. However, these findings are confounded by the demands of the position, in that those at a more advanced age were more likely to serve in more challenging management positions.

Rehospitalization after TBI

Occupation and social reintegration can be affected by medical complications that require rehospitalization. TBI impacts the central nervous system (CNS) and numerous other organ systems due to the traumatic mechanistic nature of injury, such as motor vehicle accidents, falls, and so on. This has a significant impact when injury is sustained at an advanced age. Falls are the predominant cause of injury in the elderly population.[26] The proportion of unfavorable outcomes increases with age.[27]

In a large study of all hospitalized individuals with TBI, five age groups were compared for rehospitalization within 1 and 3 years (<15 years, 15–24 years, 25–49 years, 50–64 years, and 65+ years).[28] As age at injury increased, so did rehospitalization from 6.3% in the youngest group to 37.3% in the oldest group. The range was from 11.1% in the youngest group to 56.1% in the oldest group within 3 years. Some variation within age groups existed for men versus women. In this same study, discharge to home with services was most common for those under age 15 at 88%–90% and steadily decreased across the age groups to 35%–44% for those 65 years and older. Conversely, those transferred to another facility or to a long-term care facility increased with age.

Another study comparing younger and older individuals after TBI found complication rates to vary with intracranial hypertension more common in younger individuals and urinary tract infection rates higher in older individuals.[29] Additional differences nearing statistical significance (selected at $p = 0.01$) were seen for seizures and cardiopulmonary arrest occurring more in the older group ($p = 0.022$ and 0.036, respectively). There is evidence of differences in self-reported health outcomes between individuals who are injured as younger versus older adults. Although both groups reported more health-related problems than uninjured controls, younger individuals reported more difficulty falling asleep and older individuals reported more difficulties with neurologic and metabolic/endocrine problems.[28]

An early review of medical complications and associated injuries provides valuable insight into different types of cerebral and systemic complications in TBI.[30] These authors

reported differences in outcome as measured by Disability Rating Scale scores[31] and length of stay for both acute and rehabilitation hospitalization related to severity of intracerebral and extracerebral injury and observed complications. Of individuals studied, 68% had one or more intracerebral hemorrhages. Other cerebral complications included intracranial hypertension, cerebrospinal fluid leak, hydrocephalus, and seizures. Extracerebral complications included respiratory failure, pneumonitis, urinary tract infection, soft tissue infection, coagulopathy, renal failure, and septic shock. Associated injuries included fractures, cranial nerve injuries, hemothorax/pneumothorax, intra-abdominal injury, spinal cord injury, peripheral nerve injury, brachial plexus injury, and amputation. The frequency of these complications is shown in Table 33.1.

Hydrocephalus and seizures appear to particularly have an impact on the long-term medical status of people with TBI. It could be argued that respiratory and coagulopathic complications might reasonably bear some long-term medical importance for persons with TBI.[32] It is less clear that early infectious complications, once resolved, impact long-term neurological status.

Rehospitalization can be predicted by male gender, older age, greater injury severity, etiology of injury as fall, and having additional mental or physical health conditions.[33] In this large study, it was found that 23% of all hospitalized individuals with TBI were rehospitalized within 1 year, and 35.5% were rehospitalized within 3 years after the index injury. A report of rehospitalizations was conducted 1 and 5 years after TBI for 1,547 consecutive cases[34] enrolled in the NIDRR Model Systems for Traumatic Brain Injury. Of these, 799 were eligible for 5-year follow-up. The authors reported findings that were similar to those of Cifu et al.[35] in that rehospitalization for seizures and psychiatric problems increased from year 1 to year 5, peaking at 15% in year 3 (Table 33.2).

A separate study by Marwitz et al.[34] found seizure rehospitalization rates at 18.7% at year 5. It is interesting to note that, between the two studies by Cifu et al. and Marwitz et al., rehospitalization rates for general health maintenance increased over the time periods studied. Clearly, disabled persons are less able to participate in their own health maintenance at the level seen in the general population, and general health may be an issue of concern in the discussion of aging. In persons who have sustained TBI, cognitive, social, financial, and physical disabilities may serve as barriers to self-initiated health maintenance activities and practices.

Psychiatric issues also pose a substantial concern for the aging TBI population. Although rehospitalization rates for psychiatric issues appear to remain stable from year 2 (15.3%) to year 3 (15%)[36] and year 5 (16%),[34] the incidence of self-reported TBI in psychiatrically hospitalized individuals is reported at 66%.[37] Psychiatric rehospitalization is correlated with substantially more aggression toward family members and caregivers between years 1 and 5 postinjury.[38] Specifically, Brooks et al.[38] reported the incidence of threats of violence at a rate of 15% at year 1. By year 5, these incidents were reported by 54% of caregivers. Physical assault of a family member was reported by 10% of caregivers in year 1 and 20% in year 5.

Other major causes for rehospitalization are respiratory complications and orthopedic conditions. Englander et al.[39] reported that respiratory complications were seen in 39% of 637 individuals during acute hospitalization. More detailed information was available from this study pertaining to

Table 33.1 Complications associated with traumatic brain injury

Extracranial complications	Intracerebral complications	Associated injuries
Respiratory failure 39%	Hypertension 20%	Fractures 62%
Pneumonitis 26%	Seizures 17%	Cranial nerve 19%
Urinary tract infection 21%	Cerebrospinal fluid leak 8%	Hemo/pneumothorax 11%
Soft tissue infection 16%	Hydrocephalus 5%	Intra-abdominal 7%
Coagulopathy 5%		Peripheral nerve injury 2%
Septic shock 3%		

Table 33.2 Reasons for rehospitalization by year postinjury

Reason	Year 1[a] (*n* = 79, 22.5%)	Year 2[a] (*n* = 59, 21.0%)	Year 3[a] (*n* = 40, 20.0%)	Year 5[b] (*n* = 75, 17.0%)
Rehabilitation	3 (3.8%)	0 (0%)	0 (0%)	1 (1.3%)
Seizures	8 (10.1%)	8 (13.6%)	6 (15.0%)	14 (18.7%)
Neurologic disorder	4 (5.1%)	8 (13.6%)	2 (5.0%)	2 (2.7%)
Psychiatric	5 (6.3%)	9 (15.3%)	6 (15.0%)	12 (16.0%)
Infectious	9 (11.4%)	10 (16.9%)	3 (7.5%)	6 (8.0%)
Orthopedic/reconstructive	35 (44.3%)	14 (23.7%)	10 (25.0%)	10 (13.3%)
General health maintenance	11 (13.9%)	10 (16.9%)	9 (22.5%)	27 (36.0%)
Unknown	4 (5.1%)	0 (0%)	4 (10.0%)	3 (4.0%)

[a] Cifu et al.[35]
[b] Marwitz et al.[34]

upper extremity fractures (humerus, radius, or ulna), which occurred in 11% of the study population, and pelvis or lower extremity fractures, which occurred in 21% of persons studied. Rehospitalization rates for orthopedic/reconstructive procedures remained surprisingly high in the first 3 years postinjury, ranging from 44.3% in year 1 to a relatively stable 23.7% to 25% in years 2 and 3, respectively. The likelihood of orthopedic procedures increases with age due to age-related changes in bone microarchitecture increasing the potential of fragility fractures.[40,41]

In summary, the rehospitalization data, up to 5 years postinjury, suggests that neurological and psychiatric/behavioral disorders, in addition to maintenance of general health, are issues of concern. Acute hospitalization complications and relatively short-term rehospitalization rates out to 5 years provide limited insight into likely neuromedical concerns for a population that can be reasonably expected to live from 10–55 years postinjury.[42] Currently, it is difficult to determine the full impact of TBI decades later. There is still a need for more studies looking at outcome beyond 10 years.

Mortality and life expectancy

One of the most frequently asked questions by those affected by TBI is the impact that TBI has on life expectancy. This issue presents a number of pragmatic concerns for families of people with TBI and bears on the development of suitable support systems that will be able to effectively address lifelong issues.[43] Logistical and financial planning for the individual and public health planning on a larger scale require the most accurate appraisal possible of what will need to be provided for an individual living with TBI and for how long.

Much of the literature on mortality after TBI in adults has focused on predictors of early mortality, i.e., less than 1 year after injury. Mortality studies involving hospitalized individuals with TBI have found approximately 90% survival at discharge.[44,45] Risk factors, such as age, admission Glasgow Coma Scale score, associated injuries, hypotension, hypoxia, and intracranial hemorrhage, are associated with survival.[46] Most relevant to issues of aging are studies reporting on mortality and life expectancy beyond 1 year after TBI. In a study of Vietnam veterans with penetrating cerebral injuries, the causes of death after TBI appeared to have similar patterns to those seen in the general population as soon as 2 years postinjury.[47] However, earlier studies implicated seizures as a cause of death unique to the TBI population.[48,49] More recently, seizures appeared as the third leading cause of death in reviewing a California database analyzing post-TBI mortality.[32] However, in this study, both circulatory and respiratory causes of death were more common than seizures, and both of these causes appeared consistently over time and across populations.

Overall, a few studies do suggest that life expectancy for individuals with TBI is shorter than for those in the general population.[42,49,50] However, the evidence explaining why life expectancy is shorter is very mixed.[47,51–53] In persons who have sustained severe TBI and are considered "low functioning" or dependent, life expectancies seem to be much shorter. The Multi-Society Task Force on PVS[54,55] in a literature review of the medical aspects of the persistent vegetative state examined data available on survival. The review concluded that a reduction of life expectancy to approximately 2 to 5 years for both children and adults resulted when neurological injury was severe enough to produce PVS.

In contrast, two studies of "highly functioning," ambulatory adults suggested that life expectancy was reduced by 3 to 5 years.[48,49] Roberts[56] followed approximately 500 individuals with severe disabilities up to 25 years. An estimated reduction in life expectancy of 4 to 5 years was found among individuals who became mobile enough to walk unaided. Strauss et al.[42] reviewed life expectancies across all severity levels of TBI. They also found diminution of life expectancy to be dependent upon level of mobility. That is, life expectancy for people with no mobility ranged from 10 to approximately 15 years depending upon age at the time of injury. The shortest life expectancies were associated with higher age at injury. This trend remained stable for people with poor mobility and fair-to-good mobility. Those with poor mobility ranged from 17.9 to 34.2 years life expectancy, and those with fair-to-good mobility ranged from 26.5 to 54.8 years life expectancy, again depending upon age at injury. Causes of death reported by Strauss are similar to those reported by Roberts.[56] Although Roberts reported that causes of death for people with TBI were not very different from the general population for many cases, some stood out as being different. These included meningitis, epilepsy, accidents, suicides, and respiratory disease. The causes of death reported by Roberts and Strauss et al. closely follow the causes for rehospitalization reported by Cifu et al.[35] and Marwitz et al.[34] These studies are beginning to lend credence to the concept of function as a predictor of mortality. Knowledge of objective functional measures at selected postinjury times, such as rehabilitation admission and discharge, may offer predictive value of life expectancy, neurological complications, and relevant comorbidities.[57] Accordingly, functional status has been explored in the literature as a risk factor of TBI mortality. In particular, feeding and mobility are reported to be major determinants of life expectancy in both children and adults.[42] Similarly, Shavelle et al.[32] reported a higher mortality ratio in TBI nonambulatory individuals compared to TBI individuals that were ambulatory.

In a study comparing life expectancy of children in vegetative and minimally conscious states, differences were noted for life expectancies as less impacted for those children whose etiology was TBI than for perinatal or genetic etiologies, such as congenital anomalies, Down syndrome, other chromosomal abnormalities, metabolic disorders, degenerative disorders, or others.[58] Definitions used in this study for mobility and minimally conscious state were somewhat problematic, compromising the generalizability of the work. Similarly, data was drawn from institutionalized

populations. The population mix included only a small proportion of known TBI etiology at 4.4% of more than 5,000 subjects. Consequently, life expectancy determinations for children with TBI receiving noninstitutional care today cannot reliably be deduced from this work.

At the other end of the spectrum is work examining mortality of elderly individuals after TBI.[59] This small study examined the characteristics of individuals who died between 1 and 5 years postinjury compared to a group who did not die via chart review. The deceased group differed from the control group by abnormality of gait and respiratory medications at admission and at discharge. Deceased individuals were more likely to be prescribed diabetic medications, and controls were more likely to be prescribed cholesterol-lowering drugs. Medical comorbidities present at the time of injury contributed to cause of death in at least half of those who died, suggesting a need for ongoing management of comorbid health conditions postinjury. Given cognitive, communicative, and physical limitations associated with TBI, the ability of injured elderly to seek and comply with primary medical treatment must be called into question. Routine assessment by primary medical personnel may become ever more important after TBI, to both manage conditions and potentially accommodate or slow the degenerative effects of brain injury.

There appears to be some reduction in life expectancy related to TBI associated with other comorbidities. In a study examining post-World War I head-injured veterans, Weiss et al.[53] found that the occurrence of posttraumatic seizures was a prognostic factor for a higher death rate after the age of 50 years. Although other indicators of injury severity did not lead to differences in death rates, there were significantly more deaths due to cerebrovascular causes in the head-injured group compared to controls. In post-World War II studies, Corkin et al.[52] found that penetrating head injury coupled with posttraumatic epilepsy shortened life expectancy in persons who survived the initial postinjury period when compared to head injury alone. Walker and Blumer[60] also found the death rate of World War II veterans with posttraumatic epilepsy to be higher than that of normal men. In addition, wounds involving the right cerebral hemisphere seemed to shorten life span more than similar injuries of the left hemisphere.

Finally, medical–legal issues encompassing life expectancy and the need for long-term planning seem relevant.[61] The logistics and costs of these long-term planning considerations are immense.[43] The anticipated progression of communicative, physical, and neurobehavioral changes over a lifetime is not yet an exact science. Planning for later life events and end of life can be furthered to a degree by not only the knowledge of neuromedical complications and long-term issues, but also recognition of associated functional changes arising from either the neurological injury or associated non-neurological injuries.[43]

Estimating life expectancy in a "specific" person with TBI is a complex and challenging endeavor. Statistical methods are often valuable in making life expectancy estimates for persons with spinal cord injury and other neurologic disabilities when grouped by particular characteristics. However, in a heterogeneous TBI population characterized by different injury types and severity with discrepant neurologic and functional disabilities, statistical methodology may be inaccurate.

This is further complicated with potential difficulties in communication. Engaging in outpatient medical treatment requires that the patient be able to participate well in interactions with medical professionals. To that end, communication must be accurate and precise. The ability to recall one's status in the days, weeks, or months before an appointment can be critical to determination of a diagnosis or efficacy of a chosen treatment. Similarly, adherence to medication or other treatment regimens will necessarily impact outcome. Since many individuals experience decrements in prospective memory and organizational skills, compliance can be problematic. Compounding this is the fact that many physicians are reluctant to undertake careful medication compliance review with patients, resulting in a lack of focus on medication compliance.[62]

Furthermore, the impact of pre- and comorbid variables as well as different rehabilitative and long-term supportive care paradigms may also have a differential impact on long-term morbidity and mortality. In an article by Kraus reviewing accuracy of life expectancy estimates in life care plans, it was felt important to consider nonbiographical and noninjury factors as well as the injury itself.[63] This article emphasizes a host of important variables, such as income and access to health care, which may impact life expectancy.

IMPACT OF AGE-RELATED CHANGES ON LONG-TERM NEUROLOGICAL OUTCOME

Tissue loss

As the brain ages, there is some softening and loss of cerebral tissue (i.e., encephalomacia). Encephalomacia occurs in a regional and sex-dependent manner.[64] Neurodegeneration, due to encephalomacia and vascular insults, will promote ventricular enlargement (i.e., ventriculomegaly). Aging-related ventricular enlargement is unusually attributed to ependymal cell loss and the formation of glial scars over time.[65–67]

These normal decreases in brain stiffness may be accelerated in the chronically aging TBI. Computerized tomographic (CT) volumetric studies of the cortical/subcortical mass-to-ventricular size ratio have shown that marked encephalomalacia occurs over many years postinjury.[68,69] As the processes of neurodegeneration and gliosis associated with injury advance over time, cortical and subcortical volume decreases. Concurrently, these changes are associated with increases in ventricular size. Over time, the CT pattern in TBI is one of mild-to-moderate ventricular enlargement and normal sulcal prominence.[70] Ventriculomegaly may not be as evident in cases of a focal injury. Volumetric measures

of brain morphology show that the generalized effects of most traumatic diffuse axonal injuries (DAIs) are more evident via ventricular dilatation. In contrast, the effects of focal and multifocal injury appear to be more evident in cortical atrophy measures.[69] Magnetic resonance imaging (MRI) of aged persons with a history of DAI demonstrates progressive atrophy within the corpus callosum over many years.[71,72] The process of ventriculomegaly stretches fibers in the surrounding regions, thereby impairing function.

Ventricular enlargement not only will lead to cognitive impairment, but it may also interfere with proper diagnosis and treatment of hydrocephalus, which implies an active obstruction of cerebrospinal fluid or diminished reabsorption. In other words, the differentiation between ventriculomegaly and hydrocephalus is likely to be more challenging in chronic TBI due to the effects of aging.[73] In addition, the classic triad of normal pressure hydrocephalus—impaired gait, urinary incontinence, and dementia—may also be harder to discern as these symptoms are also common in the aged.[74–76]

Age-related change in remyelination may contribute to the pathogenesis of certain degenerative conditions or to an overall diminution of neurologic function with aging. Remyelination in the brain changes with advancing age, becoming less efficient. Oligodendrocyte progenitor cells are recruited at a decreased rate as age advances as does the rate at which oligodendrocytes differentiate into remyelinating ones.[77] In some individuals, a coincidental decrease in growth hormone production, key to oligodendrocyte genesis and function, may contribute to compounding decrements in remyelination. Remyelination is dependent upon cholesterol availability within the CNS and is also impacted by decrements in neuroendocrine function. Oligodendrocyte loss arising from the original injury will predispose the brain to decreased remyelination capacity. The majority of remyelination is due to oligodendrocyte function although some contribution is made by Schwann cells in the lesion area when astrocytes are absent and in the vicinity of blood vessels.[77] Myelin repair in the CNS requires as much as half the brain energy expenditure. Impairments of energy transduction within the CNS after injury may impact energy availability for myelin repair. Myelin provides for axonal protection; thus, axonal vulnerability is higher when myelin integrity is compromised.

Cognitive decline

Cognitive changes occur as part of normal aging. Whereas some cognitive domains are more resilient to aging, others, such as processing speed and memory, are more likely to be affected.[78] The possibility of worsening of cognitive functions and the development of dementia increases with advancing age.[79] It has been estimated that there is some degree of intellectual and cognitive dysfunction affecting approximately 15% of the population over the age of 65.[80] Tissue degeneration is one of the main contributors in age-related cognitive decline.[81,82] Imaging studies have demonstrated a strong relationship between intelligence measures and brain volume in normal adults.[83–85] The relationship between intracranial volume and cognitive abilities is maintained in later life.[86] Moreover, a large study found that at age 73, earlier cognitive function and current brain volume served as a predictor of current cognitive abilities.[87] Correspondingly, more brain activation is required in older adults to perform the same task as in younger adults, suggesting that compensatory processes are being utilized to maintain function. This effect of hemispheric asymmetry reduction in older adults has been coined the "Harold effect."[88] In effect, studies in functional MRI have shown that there is a change in network connections during normal aging that is exacerbated with brain injury.[89]

Evidence suggests that TBI poses a significant risk factor for dementia as aging occurs.[90] Most likely the co-occurrence of factors associated with aging and TBI contribute to the development of dementia. One of these is the loss of brain volume as indicated above. The rate of tissue loss gradually increases with normal aging[91] and is further accelerated in the case of Alzheimer's disease (AD).[92] Similarly, following TBI, brain volume loss can occur at an accelerated rate compared to normal aging.[93,94] In accordance, tissue loss is associated with injury severity, and poor recovery as indicated by the Glasgow Outcome Scale injury severity.[95,96] There may be an optimal size range for specific brain structures, such as the hippocampus[97] and frontal regions.[98] The hippocampus has been correlated with intellectual coefficient[99,100] and plays a critical role in memory and information processing. In point of fact, a large hippocampal volume appears to offer protection from dementia.[101] The hippocampus is particularly vulnerable during aging[102] and is also likely to be affected by TBI.[96] This implies an increased likelihood of developing memory impairments when one ages after suffering a TBI.

Interestingly, it appears that some individuals with TBI may accommodate to some level of decrement in cognitive performance over time. Goldstein et al.[103] reported that, although deficits in cognitive performance persisted over time for persons with TBI, when compared to a normal population, the magnitude of the difference in cognitive performance between these groups remained stable over time. Similarly, Ashman et al. evaluated the degree of cognitive decline seen within 2 to 5 years of injury for a group of individuals with TBI aged 55 years and older compared to a noninjured, age-matched group.[104] Neither group demonstrated any significant decline in cognitive performance over the period of study although there were clear differences in overall cognitive performance between the two groups. These findings suggest that the effect of TBI on cognitive performance is additive to declines in cognitive performance associated with normal aging.

Other age-related factors

TBI has been associated with neuroendocrine dysfunction in both the acute and chronic states.[105–109] Neuroendocrine

disruptions following TBI are discussed in detail in several chapters in this text. Neuroendocrine dysregulation will impact glycolytic energy metabolism, autonomic responses, immune function, stress, neuroplasticity, and sleep.[110,111] Given the multiple and diverse functions of the neuroendocrine system, alterations in hormonal regulation will have a significant impact in long-term outcome. In addition, it is important to be aware that significant hormonal changes occur with normal aging.[112–114] Thus, aging-related hormonal effects will interact with TBI-induced endocrine dysfunction, leading to an array of chronic physical, neurobehavioral, and functional disabilities. Among the consequences of age-related hormonal changes is the effect that they will have on sleep.[115]

Sleep plays a critical role in cognitive capabilities and emotional stability.[116,117] The relationship between sleep and neuroendocrine function is bidirectional. Sleep critically interacts with several neuroendocrine axes to regulate hormonal release.[110,118–120] Given that numerous functions are hormonally regulated, the influence of sleep on overall well-being is extensive. The relevance of sleep[110,111] in recovery after TBI is notable as it affects how information is perceived and processed. Sleep changes are frequently observed as part of the normal aging process. Age-related changes include excessive daytime sleepiness, fatigue, and circadian disruptions. To further complicate matters, sleep disturbance is a common complication following TBI.[121–123] Multiple studies have demonstrated that sleep-related abnormalities are common following TBI. Abnormalities include both breathing- and non-breathing-related sleep disturbances (Table 33.3). Although sleep abnormalities are more common during the first year following TBI,[124] they are also prevalent during chronic periods. A recent study indicated that 66.7% of chronic patients present with a sleep disorder.[125] Although one can speculate, it remains unknown how TBI impacts sleep disturbances in the aged population. These impairments are likely to have a negative impact on recovery. Moreover, it has been observed that sleep pattern abnormalities following brain injury are associated with cognitive deficits.[126–129] The combined effects of reduced physical activity levels and neuroendocrine dysfunction that lead to increased adiposity may portend the development of weight-related obstructive sleep apnea.

The CNS appears to become less isolated from peripheral inflammatory processes after brain injury and, in general, with aging. As indicated within this chapter and others in this text, inflammation will contribute to tissue loss and decreased connectivity within the brain. Alterations in blood–brain barrier (BBB) permeability interact with microglia activation, proinflammatory cytokine, and reactive oxygen species (ROS) production and accumulation of toxic substances behind the BBB. Microglia are long lived and, as such, are known to be especially vulnerable to the effects of age. Alterations in BBB permeability interact with microglia activation, proinflammatory cytokine, and ROS production and accumulation of toxic substances behind the BBB. The CNS appears to become less isolated from peripheral inflammatory processes after brain injury and, in general, with aging.

Table 33.3 Incidence of sleep-related disorders following traumatic brain injury

Sleep-related disorders	Incidence after TBI
Insomnia	More than 50% of TBI patients[121] 30% of postacute brain injured patients[130] 26.7% of TBI patients[125]
Fatigue	More than 50 of TBI[121]
Hypersomnia	6.7% of TBI patients[125]
Breathing-related apnea/hypopnea	47% of TBI patients[131] 11% of brain injury patients[132]
Limb movement disorders	25% of brain injury patients[132] 3.3% of brain injury patients[125]
Delayed sleep phase syndrome	10% of brain injury patients[125]
Irregular sleep–wake disorder	3.3% of brain injury patients[125]
Poor sleep quality (more awakenings, circadian disorders)	More than 50% of TBI patients[122,123,133] 16.7% of TBI patients[125]

CHRONIC TBI AND NEUROLOGICAL DISORDERS

Impact of reserve

The concept of reserve is particularly relevant when attempting to understand the interplay between TBI and neurological disorders associated with aging. Although frequently utilized within the context of aging, brain reserve originally applies to the capability of protecting against insults to the brain regardless of etiology.[130] On the flip side, reserve may also indicate an increased vulnerability for poor outcome during normal aging as well as other insults to the brain. For our purposes, we will not limit the concept of reserve to that of "cognitive reserve," which has been utilized to describe preexisting cognitive processes as compensatory tools.[131] Instead, when referring to reserve, we will also include physical, environmental, and genetic factors that contribute to outcome after brain injury. It is imperative to consider the concept of reserve when addressing neurological disease and chronic TBI.

Numerous attempts have been made to determine whether TBI is associated in some fashion with the onset of other neurodegenerative diseases. A number of challenges exist in attempting such determination, not the least of which is the fact that the majority of injuries to the brain go unheralded. The authors suggest that inadequate medical attention and medication compliance may contribute to differences in medical complications for elderly

individuals after TBI. Although awareness of MTBI, for example, is improving, MTBI has been suspected as going unrecognized in the majority of instances of its occurrence. Consequently, understanding the true incidence of MTBI has been difficult, and accurately determining the contribution of MTBI to a host of conditions may be elusive.

Alzheimer's disease

The contribution of TBI to the development of AD has been a topic of considerable focus in the literature. It is necessary to consider the scientific limitations in research design and methodology when examining the relationship between TBI and AD. Much of the literature provides retrospective reviews of coincidental diagnoses and the development of AD or other dementia.

Several retrospective and case-controlled studies demonstrated a higher incidence of AD in individuals with a history of TBI.[132–134] Salib and Hillier[135] examined the relationship between TBI and AD and other dementias, looking at relative risk/odds ratios. Although there was an association found between a history of TBI and the development of AD (only in males) and other dementias, greater risk ratios were observed for other dementias rather than AD. In this study, head trauma was not identified to be a significant risk for AD. The interval observed between TBI and the development of AD was several decades. The increased risk of AD in men following TBI was also observed in a meta-analysis of case control studies. This meta-analysis failed to find this risk in women.[133] Another retrospective study corroborated variability due to sex but also included age and education as confounding variables.[136]

Several cohort studies failed to show strong evidence linking TBI to AD.[132,137,138] A more profound consideration of factors influencing reserve, or the lack thereof, may provide clarity in this issue. Illustrative of how reserve plays a role in the development of dementia is the overall burden of white matter damage as a TBI patient ages. White matter burden may increase over time, particularly if low-grade neuroinflammatory processes are occurring. This may set the stage for dementia in later life following a TBI earlier in life.[139,140]

Reserve in TBI is also provided by genetic factors.[141] Genetic factors influence brain structure and cognitive capabilities.[142] This is particularly evident in the case of AD. The apolipoprotein E type 4 allele (APOE-4) has been identified as a predictor of AD.[143,144] The APOE gene encodes a cholesterol-carrying protein and modulates inflammatory responses.[145] This gene has three allelic forms that can result in six potential genotypes. These are ε2, ε3, and ε4. The ε4 allele is associated with an increased risk of AD. Approximately 25% of the population carries it.[143] The fact that 25% of the population does not develop AD underlies the complexities of different contributing variables. There are multiple other polymorphisms that will have an influence on outcome. Of interest is a finding of an inverse relationship between free testosterone levels (FTL) and the development of AD in a 19-year longitudinal study of 574 men.[146] Total testosterone and sex hormone binding globulin (SHBG) were not associated with the development of AD, and the occurrence of reduced FTLs preceded the diagnosis of AD. In support, an earlier case study reported deleterious effects on Mini Mental State Examinations of testosterone deprivation in a man with a diagnosis of metastatic adenocarcinoma of the prostate.[147] Further, an inverse relationship between serum total testosterone, free testosterone, and SHBG were observed to be inversely correlated with serum amyloid beta peptide 40 in 28 community-dwelling men aged 59–91 years.[148] Taken together, these findings may underlie the finding of an increased incidence of AD after TBI in men but not in women. Finally, in a recent study of chronic traumatic encephalopathy (CTE), a subset of subjects met criteria for a diagnosis of CTE and AD. In these individuals, Aβ plaques and total levels of Aβ1-40 were increased at sulcal depths compared to gyrus crests.[149]

We previously indicated that there is debate over the link of TBI and AD. Fittingly, although this allele is associated with a poor outcome after TBI, there is not sufficient evidence to indicate that it is linked to AD-specific biomarkers and atrophy. Instead, APOE 4 and TBI appear to have an additive effect that increases the risk of AD-like symptomatology. A study evaluating 2,233 subjects indicated that only TBI patients presenting the APOE-4 allele are at increased risk of developing AD.[150] This allele has also been observed to affect outcome in younger patients. It was associated with longer duration of unconsciousness, coma, and poor function at 6 months after TBI.[151–153]

One of the classical biomarkers for AD is the peptide, beta amyloid (Aβ), which is the major component of the observed amyloid plaques that are prevalent in AD.[154] Cleavage of the amyloid precursor protein (APP) results in the formation of Aβ40 and Aβ42.[155] This is a peptide that can lead to increases in calcium release, inflammation, and consequent cellular death.[156,157] It also contributes to the formation of plaques.[158] Both human and animal studies have reported increases of Aβ42 after severe TBI.[159–161] The production of beta-amyloid plaques has been found to occur within hours of injury to the brain.[162,163] Surgically resected temporal cortex from survivors of severe TBI shows presence of beta-amyloid plaques,[164] suggesting that plaque formation is initiated quite soon following injury and in relation to the rapid upregulation of APP.

It should be noted that the increased expression of APP does not imply that amyloid plaques will develop. Whereas axonal injury occurs in the majority of TBI, including those injuries categorized as mild, only a fraction of severe TBIs show beta amyloid plaques. APP is a ubiquitously expressed glycoprotein that is synthesized in normal neurons and transported axoplasmically.[165] Moreover, it is widely utilized as a reliable marker of axonal damage. Increases in APP are associated with acute neuroinflammtory responses.[166,167] According to postmortem studies, only 30% to 50% of cases of severe TBI show the presence of diffusely distributed beta-amyloid plaques.[162,168] As detailed earlier, TBI is

an environmental trigger for the upregulation of Aβ. For those individuals who develop AD after a TBI, there is an over-representation of the APOE-4 allele.[169] However, as indicated earlier, not all who possess the APOE-4 allele are destined to develop AD.

In addition to amyloid plaques, the appearance of neurofibrilliary tangles (NFT) is considered one of the classical histopathology markers for AD.[170] NFTs consist of aggregations of tau protein within neurons. Tau protein's main function is to stabilize microtubules. However, when hyperphosphorylated, it leads to the formation of tangles. Tauopathies are also observed in other forms of dementia. Within the context of TBI, tauopathies are predominantly observed following cumulative TBIs. The presence of NFTs has been identified in the brains of boxers who suffered from a form of dementia that was initially identified as being "punch drunk" or having dementia pugilistica. It has recently been recognized as CTE.[171,172]

The literature on CTE continues to evolve. CTE takes at least two forms and perhaps more. The two more commonly characterized forms include one that appears primarily psychiatric in nature with behavior and mood disorder and paranoia and a second that is primarily cognitive in nature.[173] Some cases of CTE involve motor neuron disease, resembling PD. Some authors view CTE as a condition that appears to progress in four stages.[172] Stage 1 is comprised of headache and loss of attention and concentration; Stage 2 is comprised of depression, explosive behavior, and loss of short-term memory; Stage 3 is comprised of executive function compromise and cognitive impairment; and Stage 4 is comprised of dementia, word-finding difficulty, and aggression.

As one attempts to draw conclusions regarding TBI and its relationship to the development of AD or other dementias, multidimensional factors need to be considered. The clinician must evaluate the potential interrelationships between age, neuroendocrine function, various neuropathologies associated with different injury types, idiopathic neuronal atrophy, the potential contribution of repetitive trauma, genetic predisposition, and immunosusceptibility. These relationships may all play a role in the timing of the onset of dementia, the rapidity of progression of dementia, and/or the development of other neurodegenerative disorders.

Epilepsy

Seizures (i.e., ictal episodes) are a serious concern as they can aggravate existing cognitive deficits observed in dementia.[174] Here, we discuss seizures within the context of aging with a TBI. This topic must consider the interaction between TBI and aging-related normal processes as well as neurological diseases. Seizures play a relatively prominent role in a discussion of either aging or TBI. Seizures represent the second most frequent intracerebral complication, occurring at a rate of 17%. Only intracranial hypertension, as an intracerebral complication, is higher and then by only 3%.[30] Seizures increase in frequency from year 1 to year 5 as a reason for rehospitalization and become the second most common reason for rehospitalization, following general health maintenance.[34,35] Here, we focus on seizures as a long-term consequence of TBI. More information on seizures and TBI can be found in other chapters in this text.

Seizure incidence appears to be highest in children. Interestingly, there appears to be a U-shaped relationship between seizure incidence and age.[175–177] In other words, although the incidence of pediatric seizure decreases over time, the incidence of adult seizures appears to increase with age. A prospective epidemiologic population-based study followed the incidence of epilepsy (i.e., recurrent seizures) and unprovoked seizures over a 50-year period.[175] Incidence in people over age 70 was found to be two to three times greater than in children. Incidence at age 40 was 30/100,000 and, by age 80, increased to 140/100,000. Generalized seizures occurred most frequently in children whereas the elderly had a higher incidence of partial onset seizures. In people over age 75, partial epilepsy was five times more frequent than at earlier ages. In contrast, incidence of pediatric seizures decreased as the child aged and remained stable up to age 54. This study determined that the three most common etiologies for seizure disorders in people over age 65 were cerebrovascular disease, degenerative diseases of the CNS, and CNS tumors.[175] It should be noted that seizures are fairly common within the first 2 weeks of cerebral infarction and are considered to be an acute effect of the infarction.[178,179] Degenerative diseases are also associated with seizures. The incidence of seizures in those that have a degenerative disease ranges from 10% to 22%.[174,180,181]

A noteworthy distinction between pediatric and adult seizures following TBI is when posttraumatic epilepsy (PTE) occurs. Children are more prone to show seizures during the acute and subacute periods after TBI. Conversely, adolescents and adults are more likely to show late seizures.[182] Although frequently considered as an early or subacute effect of TBI, PTE can also have its first manifestation many months or years after TBI. Although a significant amount of seizures occurs within the first year, the risk remains for over a decade.[183] However, it should be noted that a majority of individuals (approximately 95%) who remain free of seizures in the first 3 years after injury remain seizure-free long term.[184–186] This implies that certain injury characteristics are likely to increase the risk of late seizures.

Multiple studies indicate the risk of developing PTE is increased if cerebral tissue is dramatically compromised as in the case of a penetrating injury. It appears that dural penetration is a key risk factor for PTE.[182,187–190] Feeney and Walker[191] developed a mathematical model to estimate the probability of posttraumatic seizures. This classic study found individuals with central parietal injury, dural penetration, hemiplegia, missile wounds, and intracerebral hematomas to be at greatest risk for development of PTE. Accordingly, it has been estimated that the risk of

seizures following penetrating injury ranges from 35% to 53%[192] whereas the risk of seizures following diffuse–closed head injury without contusion or laceration of the cortex is approximately 5%.[193] Similar findings were observed in another study. Trauma resulting in cortical injury and neurological deficits without interruption of the dura matter had an incidence of PTE ranging between 7% and 39%. In contrast, when dural disruption and neurologic abnormalities coexisted, the incidence increased dramatically to between 20% and 57%. Interestingly, in this study, injury severity and the persistence of ictal episodes did not appear to have a correlation.[182,194] It should be noted that a severity effect was observed in a longitudinal, cohort study. This study observed that when late seizures developed following severe TBI, the probability of recurrence was high.[195]

It is always of great interest to be able to discern whether a seizure will be an isolated event or whether recurrence is likely or inevitable. This is of concern for operation of automobiles and mechanized equipment, independence and safety in the community or living environment, and return to work. Different factors that have an impact on reserve can provide information on the risk of developing PTE following TBI. For example, the coexistence of genetic predisposition must be considered. Investigation of the influence of apolipoprotein alleles in nonlesional temporal lobe epilepsy (TLE) saw no relationship between APOE polymorphisms and TLE.[196] However, a later investigation found that, although the distribution of APOE genotype was similar between temporal lobe lesional and nonlesional patients and controls, higher levels of plasma APOE were observed in TLE patients at 4.9 times greater than controls[197] suggesting that APOE may play a role in TLE.

It is important that those who develop seizure disorders after TBI have appropriate anticonvulsant therapy and thorough follow-up. Individuals receiving this level of care are more likely to attain higher rehabilitation goals and functional outcomes, such as employment.[182] Prophylactic treatment of PTE has been controversial.[198–203] Thus, a clearer understanding of risk factors should be beneficial in determining if prophylactic anticonvulsant treatment is merited. It should also be taken into account that management of seizures is impacted by physiological changes in aging.[204] Pharmacokinetics, routes of administration, drug interactions, and pharmacodynamic interactions must all be considered as they influence treatment selection.[176] Aging is associated with decreases in serum concentration of plasma proteins and albumin necessary for pharmacological binding, absorption, and bioavailability.[205,206] Inefficiencies in hepatic and renal function with advancing age will also impact metabolism and excretion.[205,206] Swallowing and cognitive decline may contribute to difficulty with an oral route of administration. Nasogastric, intramuscular, and rectal options for drug delivery must be made available.[207] Finally, in people over 60 years of age, the average number of drugs taken at one time is seven with up to 13 taken over a year.[208] The risk of pharmacokinetic and pharmacodynamic polypharmacy interactions is quite high. Drug effects are particularly complicated when TBI occurs in an aged brain. Hepatic metabolism has been shown to be altered following acute neurotrauma.[202,203] This altered metabolism following neurotrauma may persist for at least 2 to 4 weeks in some patients, and the degree of metabolic alteration appears to be associated with older age.[202,203] Time to normalization of unbound clearance is longer for patients with TBI and may be due to activation of proinflammatory cytokines tumor necrosis factor alpha and interleukin-1 and -6.[203] While managing a person with TBI over his or her entire life, the clinician must be cognizant of the unique presentations of the types of seizures that present with aging and the elderly, appropriate methods of diagnosis, and the complexity of different treatment paradigms.[207,209] Care should be taken to avoid overattribution of seizures to a history of TBI alone in the aged.

Other neurological diseases

Tissue loss, either during normal aging or TBI, involves white matter. The incidence of white matter damage increases with aging and can manifest as movement disorders with or without significant cognitive deficits. Damage to white matter will affect the efficiency of connectivity.[210–212] In turn, alterations in connectivity are associated with dementia.[213] Given that redundancy within the brain offers protection or reserve, alterations in connectivity will negatively influence long-term outcome. Correspondingly, network damage is a strong predictor of outcome after TBI.[214,215] Primary pathways are established during development and are likely to be the most energetically and functionally effective.[216] However, in the case of damage to the primary pathways, redundant pathways may enable function. However, these alternate pathways may not be as effective as the originals.[217] Given that even mild traumatic events can have an impact on connectivity,[218] it is not surprising that previous TBI events can have a negative impact on reserve. Consequently, the risk of dementia is increased with repeated injury.[219] The occurrence of CTE exemplifies this.

Numerous diseases, such as multiple sclerosis (MS), have been shown to lead to disruptions in connectivity. Although the etiology may differ between TBI and other neurological conditions, commonalities exist in that the same premorbid factors will influence functional outcome. For example, premorbid intelligence and educational level will lessen the cognitive effects of both MS and TBI.[220,221] It is well known that TBI leads to notable axonal damage as well as demyelinization.[222] Given these effects, TBI would be expected to exacerbate symptomatology in MS. However, there is a notable lack of studies involving MS patients that incur a TBI. Most of these studies have concluded that TBI and other types of injuries do not precipitate MS or lead to relapses of MS.[223–225] It should be noted that the vast majority of TBI cases included in these studies had mild injuries with minimal or no periods of unconsciousness. A large cohort study, utilizing data from the National Health Insurance Research Database, followed 72,765 TBI patients for 6 years. Patients

with TBI had a significantly higher incidence of MS compared to age- and sex-matched controls.[226]

Other diseases, such as Parkinson's, are associated with aging. Parkinson's symptomatology has been reported following TBI. It is also referred to as "pugislitic parkinsonism." However, the association between Parkinson's disease (PD) and TBI has been widely debated. Whereas some studies have found an increased risk of developing PD following TBI,[227,228] others have not.[229–231] Most likely, PD symptomatology does not develop after a single trauma but may be more prevalent after repeated trauma.[232] There is likely to be an additional risk in exacerbation of neurological illness in those patients who are at risk of PD. For example, subjects exposed to the pesticide Paraquat who had a prior TBI were more likely to develop PD.[233]

The majority of studies investigating the relationship of TBI and neurological disease have focused on brain injury as either a precipitating risk factor for the *de novo* development or exacerbation of the progression of AD, PD, amyotrophic lateral sclerosis (ALS), and MS.[223–225,231,234] A recent random effects meta-analysis supports the association of MTBI with various neurological diseases (AD, PD, ALS, dementia, and mild cognitive impairment) and psychiatric outcomes (depression, bipolar disease, mixed affective disorder, and psychotic disorder).[235] Nevertheless, it should be noted that notable limitations are present in the majority of these studies. Due to these limitations, there has been much debate linking TBI to different neurological diseases. Conflictive findings are due to diverse methodological approaches and variable heterogeneity. Moreover, whereas some studies take into consideration factors that can determine reserve or degree of vulnerability, others do not.

TBI AT AN ADVANCED AGE

As indicated within the introduction, it is important to distinguish between aging with a TBI and enduring a TBI at an advanced age. The primary cause of TBI in elderly adults is falls.[26] Due to normal aging processes, neurological burden is increased, and reserve is decreased. Thus, sustaining a TBI at an advanced age is more likely to result in a poor outcome. Animal models of TBI clearly indicate that age increases vulnerability. Aged rodents exposed to experimental TBI show significantly more neuropathology compared to nonaged rodents.[236] Correspondingly, elderly subjects who sustain a TBI usually have a worse outcome compared to nonelderly TBI patients.[237] Besides age-related neural degeneration, neurological burden may include prior neurological disease, substance abuse, and psychiatric conditions. Adult TBI patients with a neurological burden are likely to perform worse in cognitive tests compared with TBI patients that do not have neurological burden.[238] Adverse neurological history would also include prior TBI.[239,240]

The link between neurological disease and TBI at an advanced age is more difficult to determine given that neurological diseases, such as AD, tend to develop over time.[15] In addition, studies exploring the link between TBI and neurological diseases in this group of patients are further limited by tending to have a short follow-up period as well as a limited sample size.[241]

It should be noted that elderly TBI patients are still likely to benefit from either inpatient or outpatient rehabilitation.[242] This was corroborated in more recent studies in which outcome measures were compared at different ages after a comprehensive rehabilitation program.[24,243]

PREDICTIVE VALUE OF RESERVE

Prognosis in TBI has been challenging and has frequently relied on clinical experiences. However, a clearer understanding of preinjury variables can provide insight into long-term outcomes. After brain injury, a number of factors appear likely to contribute to disease processes. These include factors that are unchanging, such as gender and genetics, along with those that change across time, such as age, endocrine function, metabolic factors, physical health, and disease staging.[244] Additionally, immune system function impacted by aging, endocrine function, BBB function, and sleep can be added as potential self-perpetuating contributors to inflammation. Consequently, the individual with brain injury is more likely to experience the effects of the changing variables, making disease expression and progression difficult to predict.

Gender and genetic predisposition to certain disease processes will necessarily be impacted by the confluence of the above static and changing factors. Indications of differences in neurological disease presentation are found in varying prevalence, progression, and severity for AD and PD, attention deficit and hyperactivity disorders, and schizophrenia.[245] Gender differences are found in the presence of postconcussion syndrome following MTBI in 50% of women versus 30% of men. Disability was noted in more women than men (52% and 37%, respectively).[246] Gender differences after MTBI are not present for minors and only for adults with MTBI.[247] Although TBI is more prevalent in men than in women, the effects of injury may differ. There appears to be less difference attributable to gender in overall outcome following moderate-to-severe TBI; however, a few studies point to gender differences that emerge with older women, perhaps connected to age-related hormonal change.[248,249]

Factors that offer protection or reserve include intellectual ability, leisure activities, and socioeconomic status.[250,251] Contrarily, preinjury psychiatric and emotional disturbances are associated with increased vulnerability.[250,252] As indicated earlier, the loss of neural structures associated with TBI earlier in life does reduce overall neuronal availability and, thereby, diminishes the redundancy of neural structures. As such, a diminished reserve may contribute to an earlier manifestation of dementias. To the extent that AD and other dementias may have a genetic basis, persons with TBI may experience the development of these dementias just as they might other diseases, such as cancer or heart disease.

Likewise, detection of Aβ42 can be utilized as a predictor of outcome. Elevated Aβ42 in CSF would be indicative of an increased clearance of Aβ42, thus decreasing potential plaque load. This protective effect has been demonstrated acutely.[159] However, it should be kept in consideration that human cognition is influenced by hundreds of genes. Thus, a "good" cognitive long-term outcome following TBI is more likely due to complex polygenetic phenotypes.

The clinician considering cognitive decline must be able to differentiate normal age-related cognitive decline from early signs of dementia, especially in attempting to prognosticate and make recommendations to individuals and their families. Several studies have attempted to examine the reality, persistence, and perception of TBI-related progressive cognitive impairments with aging. It is in situations such as this when it is necessary to weigh the neurological burden, education, and other factors that contribute to reserve.

Cognitive decline may become more apparent as time progresses. An interesting factor that has been observed is that injury recovery is observed for approximately a year after injury, but around 5 to 7 years, a rapid decline can occur. This was found in a large cohort TBI study including all injury severities.[253] This study indicated noteworthy variability in long-term outcome. In particular, those persons who sustained an MTBI had a greater disability. Lingsma[254] readdressed this point and found that severity (22%) and lesion burden (15%) contributed to 37% to the variance. Demographic factors accounted for 7%. Thus, a person that suffered a TBI earlier in life may show a dramatic decrease in function as aging takes place. An explanation for this decline may be that a secondary precipitating age-related factor occurred that prevailed over the protective effects of reserve. In other words, reserve "hid" the deficits for a sustained time until they were overridden. This hypothesis is supported by studies indicating that higher education and achievement is associated with[255] detection of AD and related mortality at a more advanced age.[256] As previously mentioned, education has been demonstrated to offer protection from normal aging.[257–259]

Recently, studies examining the history of recurrent concussions and even repetitive subconcussive contacts to the head have been evaluated as risk factors in developing later-life cognitive impairment and/or AD. In a study of retired professional football players who had a previous head injury exposure, the risk of developing late-life cognitive impairments was examined by Guskiewicz.[255] This study demonstrated a dose–response relationship between concussion frequency and cognitive impairment throughout the subject's lifetime. More specifically, retired players who had sustained three or more reported concussions had a fivefold prevalence of mild cognitive impairments as a diagnosis and a threefold prevalence of reported significant memory problems when compared with other retired players who did not have a history of concussion.[260,261] As it relates to MTBI and concussion, future prospective studies were recommended. Specifically, these studies need to more clearly document the history related to type and severity of concussion, correlative rigorous diagnostic criteria, genetic evaluation, and serial clinical evaluations, including neurocognitive testing and functional neuroimaging.

SUCCESSFUL AGING

Successful aging is a wonderful goal for an individual who has endured a TBI. Successful aging is defined as an optimal state of overall functioning and well being. Successful aging can be difficult to achieve even in the general population. In a cross-sectional aging study that obtained information from 599 participants in Leiden, the Netherlands, successful aging, from a public health perspective, was defined as a state of being.[262] All participants were classified as "successful" or "not successful" based on optimal scores for physical, social, and psychocognitive functioning and feelings of well-being using validated quantitative instruments. Although 45% of the participants had optimal scores for well being, only 13% had optimal scores for overall functioning. In total, 10% of the participants satisfied all the criteria and could be classified as "successfully aged." The qualitative interviews showed that most elderly people viewed success as a process of adaptation rather than a state of being. The participants recognized the various domains of successful aging but valued well-being and social functioning more than physical and psychocognitive functioning. Therefore, aging people with TBI are not unlike the elderly population and should view successful aging as a process of adaptation.

A study conducted by Harrison-Felix et al. investigated mortality in a cohort of 2,178 individuals with TBI completing inpatient rehabilitation.[263] It was found that individuals with TBI were twice as likely to die compared to individuals in the general population of similar age, gender, and race. This resulted in an estimated average life expectancy reduction of 7 years for individuals with TBI. The strongest risk factors for death 1 year postinjury were older age, greater disability at rehabilitation discharge, and, interestingly, unemployment at the time of injury.

As a follow-up to this retrospective cohort study, "causes of death" in individuals with TBI were further investigated.[263] Databases utilized to investigate causes of death included the TBI Model Systems National Database, Social Security Death Indices, death certificates, and the U.S. population age–race–gender cause-specific mortality rates from 1994 in comparison. Outcome measurement tools were the International Classification of Diseases–9 revision Clinical Modification-coded death certificates. Individuals with TBI were 37 times more likely to die of seizures when compared with other causes. Individuals with TBI were 12 times more likely to die of septicemia; four times more likely to die of pneumonia; and approximately three times more likely to die of other respiratory conditions (excluding pneumonia), digestive conditions, and other external causes of injury.

In summary, the relative known risk of morbidity and mortality following TBI with increasing age makes it important for individuals to have vigilant follow-up and

monitoring. Specifically, the prevention, diagnosis, and optimal management of frequent comorbidities need to be monitored and managed over a lifetime while taking into consideration multiple factors that influence resilience. In others words, in order to increase the likelihood of successful aging, it is important to view TBI as a chronic disease in which pathophysiological processes will interact with age-related changes.

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34

Children and adolescents: Practical strategies for school participation and transition

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No head injury is too severe to despair of nor too trivial to ignore.

Hippocrates
Fourth century, B.C.

INTRODUCTION

Children and adolescents sustain traumatic brain injuries (TBI) of many types and severities. Regardless of the etiology or severity level, TBI is known to expose the child's developing brain to potential transient or permanent deficits in physical, cognitive, social, and behavioral domains.[1–3] Because the child's brain is still developing neuronal structures and connectivity, it is possible that already existing skills can be challenged, and emergence of skills that were not developed at the time of the injury will not take place or can be significantly delayed.[4–6] In some instances, the full effect of the injury is not known for many years after the injury.[6–8]

The challenges of returning to home, school, and community are reported to be some of the least organized and poorly supported experiences for the child or adolescent and his or her family.[1–3,6–8] Transition from an acute (hospital or rehabilitation unit) to postacute (educational unit) setting is identified as a major concern for the loss of service provision.

Discala et al.[9] followed the hospital discharge of more than 24,000 children and found that the majority of children with functional limitations were not given referrals to rehabilitation facilities following discharge from the hospital. Bedell reported that even the children and adolescents who were provided inpatient rehabilitation were less well prepared to participate in age-appropriate activities at discharge.[10,11] Recent research confirms that this disruption in service provision continues.[12,13] The result is that many children are not identified as needing services in the community. When they are identified, the majority of rehabilitation for children and adolescents is completed within the community, and the school is often the primary provider of services.

We have traditionally approached the medical, educational, and community living aspects of service provision by referring to a continuum of care. DePompei[14] suggested that viewing treatment and rehabilitation from a traditional continuum of care (Figure 34.1) that says treatment begins in the hospital and ends in the community may not be the most beneficial perspective and may, itself, be responsible for the lack of smooth transition among hospital, school, family, and community. This traditional continuum of care begins with emergency medical services caring for the injured child and transporting him or her to a hospital where trauma and medical teams in the acute care hospital provide specialized medical interventions. When stabilized, rehabilitation teams are involved in the process of treatment. At a point at which the child or adolescent is showing progress and is medically able to return home, the medical team discharges the child to home, school, and community. The responsibility then rests with community resources and parents to provide additional rehabilitation and education services and to prepare the child or adolescent for transition to community living.

DePompei believes that the continuum of care is insufficient to explain the concepts surrounding the injury and reintegration to community. An alternative to thinking about a continuum of care can be found in Condalucci's[15–18] model of community interdependence. The interdependence concept suggests that there must be an interconnection or interrelationship among two or more entities. In our case, medical, family, educational, and community entities should be responsible to interprofessionally team with one another as points of contact on the circle. The Circle of Community Interdependence (Figure 34.2) is not a linear model as is suggested by the continuum of care, but a circular concept that begins and ends in the community.

In this concept, the injury or illness begins in the community where the child or adolescent is a living, contributing member. Treatment of the child's brain injury then engages experts in medicine, education, community, and the family, who collaborate with the same goal: to return the child to where he or she began—the community. As this concept is based on a circle, any point on the circle may be the beginning point of care. The Circle of Interdependence,

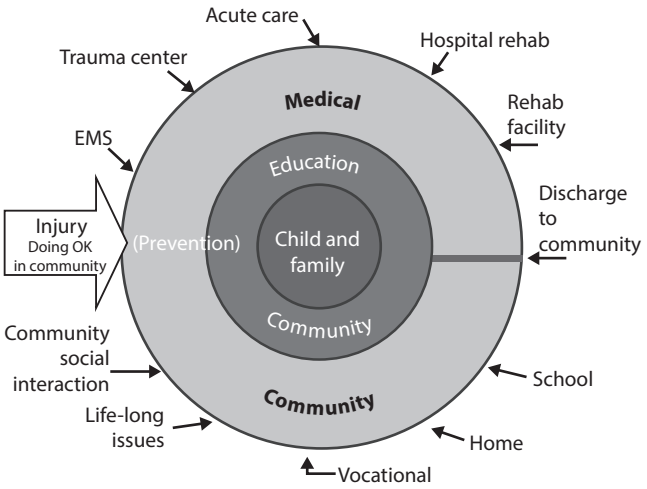

Figure 34.2 Circle of community interdependence. EMS = emergency medical services. (From Blosser, J. and DePompei, R., *Pediatric Traumatic Brain Injury: Proactive Interventions*, 2nd ed., Delmar, New York, 2003. With permission.)

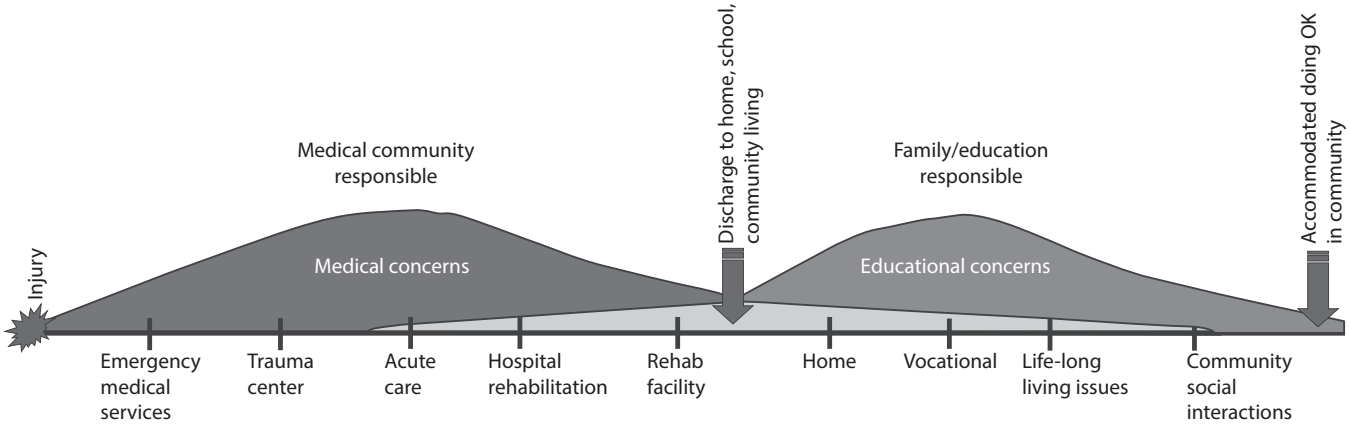

Figure 34.1 Continuum of care for youth with acquired brain injury (ABI). (From Blosser, J. and DePompei, R., *Pediatric Traumatic Brain Injury: Proactive Intervention*, 2nd ed., Delmar, New York, 2003. With permission.)

therefore, accounts for all aspects of service equally within the community. This concept is supported heavily in the literature.[19–24]

Recently, a different perspective regarding how professionals should think about aspects of service provision has come from researchers and medical personnel who indicate that TBI should be considered a chronic disease and managed as such. Masel and DeWitt[25] suggested that TBI should not be seen as a one-time event requiring no further treatment after a period of "recovery." Instead, they urge professionals to consider the World Health Organization's (WHO) definition of chronic disease. WHO states that chronic disease has one or more of the following characteristics: it is permanent; is caused by nonreversible pathological alterations; requires special training of the patient for rehabilitation; and/or may require a long period of observation, supervision, or care.[26] Authors suggest that TBI is an unfolding sequence of damage, and the following medical issues for children and young adults after TBI have been documented in the literature.[27–31]

1. Endocrine system abnormalities that result in short stature, premature development of breasts and menstrual cycle in females, aggressiveness, weight gain and hypothyroidism, and pituitary gland dysfunction
2. Onset of seizures and death from seizures
3. Premature development of Alzheimer's disease, dementia, Parkinson's disease, multiple sclerosis

If we provide services from a community of interdependence concept, we should assume responsibility for the entire circle of care regardless of which part we play in the circle. Thus, the concept that TBI is a disease process should continue into educational and community intervention. Treatment is provided with consideration of the eventual return of this child to the community, and providers in the educational and life-long living community receive the child or adolescent with an appreciation of the complex and unique medical aspects that will affect learning by this child. Using this thought process, we are better able to focus on the total needs of the child or adolescent to function within the community. When this interprofessional concept is employed by all those seeking to assist the child or adolescent, arguments for obtaining financial, social supports, and agency services can be justified.

In this chapter, we operate from two concepts—that the majority of rehabilitation for children and adolescents occurs at school and in the community and that there is a circle of community care that should guide interventions—and one concern: that the link between cognitive communication and learning is often ignored when planning for these children. If these perspectives are accepted, we can begin to plan, interactively and proactively, for this population. This chapter focuses on the following aspects:

- Describing the cognitive–communicative behaviors a student may exhibit after TBI
- Suggesting how the cognitive–communicative challenges will affect learning and behaving in the classroom
- Outlining strategies for academic and social learning in school
- Discussing laws and regulations that affect education, provision of services, and transition issues
- Providing methods to affect seamless transitions throughout the educational lifetime of the student

COGNITIVE–COMMUNICATIVE CHALLENGES AFTER TBI

Many cognitive processes can be affected after sustaining a TBI. These processes can impact learning and behaving in the classroom. The processes of attention, processing speed, short- and long-term memory, organization, and problem solving are often challenged. In addition, impulsive behaviors and receptive, expressive, and social pragmatic language skills are potentially problematic.[2,3,12,13,21,32–35] When developmental issues are also considered, challenges to learning are further confounded.

Classroom behaviors often reflect problems the student is experiencing with the abovementioned cognitive–communicative processes. Unfortunately, many teachers attempt to alter the behaviors without considering the underlying processes that are affecting the behaviors. If these underlying processes are considered in the educational process, classroom behaviors and learning can be modified. Table 34.1 outlines the cognitive processes, describes how a process can be challenged in a student with TBI, and gives examples of how these behaviors may appear in the classroom and may be affecting classroom participation. The behaviors are simply examples of what can occur in the classroom and should serve to stimulate discussion about processes that may be affecting the capacity for learning in a specific student and what behaviors might occur in a particular classroom.

When transition from hospital or rehabilitation facility to school is planned, reports are generated that usually describe challenges to the cognitive–communicative processes. Additional information should be provided in the report about what the behaviors that reflect the problem areas might look like in the classroom. Provision of such information would be most beneficial to teachers prior to a school reintegration when preplanning adequate structure and academic outcomes for the student is the most beneficial.

Another challenge when planning proactively for the student is to consider the developmental changes that may affect future growth and learning. Individuals have stated that, in the case of children and adolescents, the saying "time heals all wounds" should be "time reveals all wounds." Blosser and DePompei[33] also suggested that the child may not grow out of the disability but rather may grow into it.

Table 34.1 Cognitive processes, challenges to a student with TBI, and possible classroom behaviors

Underlying cognitive process	How process can be affected after TBI	Possible classroom behaviors
Attention	Unable to sustain or maintain attention to complete tasks or activities	Fussing with books, papers, pencils; looking out a window; bothering a neighbor; daydreaming; moving about the classroom; calling for teacher's attention about a different matter
Delayed processing speed	Much slower to respond to written or verbal directions, questions, requests Difficulty with rate, amount of complexity of information presented	Unable to formulate a response to a question in usual time allotted for students to respond even though he or she may know the correct response or behavior; speaking out; throwing paper or pencil; ceasing attempt to participate; bolting from classroom
Short-term memory	Information is not held long enough to respond to it	Unable to follow directions to locate certain page in text, sequence several requests at once, or respond to request to spontaneously change an activity
Long-term memory	Information is unable to be stored for retrieval when needed; information that is stored cannot be accessed when required	Recognizes memory strategies, such as rehearsal, but cannot use spontaneously; vocabulary learned for health on one day is not recalled the next; poor test-taking skills
Organization	Unable to move through the day in a logical manner; planning for events or tasks is sporadic and uneven, lacking a methodological means to achieve an end; inability to plan how to attack a job or assignment in a logical order	Does not recall order of the classroom day and is unprepared for class assignments or locations; begins an assignment but does not finish; offers to do a task, such as collect and sort classroom papers, but becomes lost in the details before completing the task
Problem solving	Often cannot locate alternative methods to solve a problem; believes there is only one way to approach a dilemma; disorganized in planning how to solve a problem; unable to sequence behaviors in order to resolve a challenge	Insists there is no solution to a problem; tries to solve a problem in exactly the same way for long periods of time; does not recognize suggestions of the teacher for changing a way to work a problem
Impulsivity	Speaks or acts out immediately without evidence of "thinking through" the situation	Leaves seat to sharpen a pencil when teacher is talking; tells teacher her hair is dirty and looks bad; employs socially unacceptable language or gestures
Expressive language	Difficulty with word recall; poor organization of conversation; speaks off topic; rambles; written work is equally tangential and disorganized	Uses "thing" or "you know" rather than the noun or verb; tells long, unrelated story to the class; telling or writing about how to complete a science experiment is out of order and disorganized
Receptive language	Poor comprehension of vocabulary; inability to sequence or follow multiple directions	Even though able to talk all the time, unable to follow through on what he or she is told to do; appears not to hear what teacher says and asks for multiple repeats
Pragmatic language	Difficulty with turn-taking, maintaining, and requesting in conversations; inability to monitor quality of conversation; poor comprehension of humor and puns; use of socially unacceptable words	Unable to maintain adequate social space with other students; touches the teacher to gain attention; calls out to the teacher numerous times when told to wait; keeps talking when others indicate they are disinterested; doesn't laugh at other students' jokes; can't use slang that others would accept; curses at the teacher or at peers

(*Continued*)

Table 34.1 (Continued) Cognitive processes, challenges to a student with TBI, and possible classroom behaviors

Underlying cognitive process	How process can be affected after TBI	Possible classroom behaviors
Executive functioning	Difficulty with many of the processes listed above, plus an inability to recognize strengths and weaknesses	Does not recognize when homework was completed correctly and may not do the same type of assignment well the next day; cannot outline what behaviors were successful in the classroom; does not describe what problems are experienced when trying to follow directions

As child and adolescent brains mature, the challenges of adapting to a more complex world increase. As the child grows, learning in school becomes more difficult; social and behavioral expectations increase; and adult expectations for community living, work, relationships, and quality of life emerge.[24,32] Data show that moderate-to-severe brain injury is usually characterized by increasing functional disability as the child ages and can impact the normal development that is expected. This phenomenon has been well described by clinicians and researchers, and it is variously called the "latent effects" or "neurocognitive stall" associated with pediatric TBI.[7] Thus, children and adolescents may not meet developmental milestones as they struggle with new learning and cognitive development. This neurocognitive stall may emerge despite the child seeming to have recovered cognitive abilities commensurate to his or her preinjury level.[7] Hence, as the child or adolescent grows and new learning and cognitive development does not keep pace, he or she falls further behind peers. Figure 34.3 depicts child growth, brain injury, and neurocognitive stall.

Thus, three developmental perspectives to keep in mind with this population include the following:

- A previous base of knowledge may allow the student to score within normal limits on standardized tests immediately after the injury. Over time, as new learning should happen, the student is unable to keep up with curricular demands and begins to fail. Often, parents are not aware of this potential problem, and schools do not recognize the connection to the TBI.
- Developmental milestones may not be reached as the student grows. Ability to reason abstractly, to use deductive or inductive problem-solving skills, and to organize homework for multiple teachers or subjects can be affected several years after the injury. This change in learning potential is sometimes not related back to the TBI when it occurs many years after the initial injury.
- The brain of a student is in a constantly developing and changing mode. Myelination of brain cells continues to impact learning potential for years after the injury. Thus, the student who begins to fail as pragmatic, social skills, and adult personality traits should be emerging is not often identified as continuing to have challenges as a result of a TBI that occurred years earlier, and teaching strategies that may help are not considered.

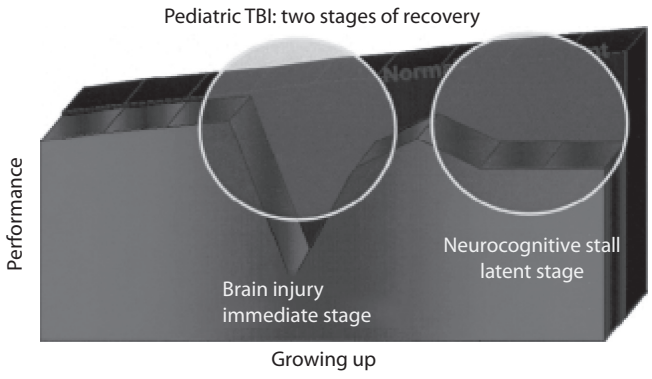

Figure 34.3 **(See color insert.)** Depiction of child growth, brain injury, and neurocognitive stall. (From Chapman, S., *Brain Injury Professional*, 3, 4, 10–73, 2006.)

Case of John

John was injured in a car crash the summer between kindergarten and first grade. He was unconscious at the scene and was hospitalized for 2 days with a diagnosed TBI and a broken leg. His preschool and kindergarten academic records indicated that he was a normally developing child with prereading and math skills intact. He was able to read introductory first-grade materials and was communicating with ease in all academic and social situations. After the crash, he entered first grade where he continued to demonstrate adequate learning skills in first and second grade. His grades were passing to outstanding in all academic areas. However, he began to stutter at the end of first grade and, by the end of second grade, had been referred to the speech–language pathologist. He began failing most academic requirements for reading and language arts in the third grade and, by fourth grade, was referred to special education for

Case of John (Continued)

a complete evaluation. School personnel considered him to be learning disabled (LD), and no reference to the TBI was made in any evaluation. There were no assessments of cognitive processing completed.

John is an example of a youngster who performed well after his initial injury on previously learned information but failed to meet developmental milestones as he grew. As there was no annual evaluation in place, his learning difficulties were not recognized until they became severe, and interventions that may have facilitated learning were not instituted in a timely fashion. When the problems were recognized, the association with the TBI was lost and he was diagnosed as LD rather than TBI.

EFFECT OF COGNITIVE–COMMUNICATIVE CHALLENGES ON LEARNING AND BEHAVING IN THE CLASSROOM

Interrelationship of language, executive functioning, social pragmatics, and self-regulation for a child with cognitive–communicative problems

Singer and Bashir[36] discussed the concept that language, executive functioning, and self-regulation (behavior) are interrelated and emphasized that employing metacognition for academic success is critical. They stated that the role of language in both executive functioning and the self-regulatory process is not yet well acknowledged but is essential to both processes. Vygotsky[37] stated that speech plays a central role in the development of self-control, self-direction, problem solving, and task performance. He argued that speech is learned in the course of social interaction and is the medium for learning and knowing how to regulate personal behavior. Wertsch[38] and Bashir, Conte, and Heerde[39] suggested that children learn appropriate language and, then, use verbal scripts to regulate thinking that guides participation in the learning and communication demands of school. Children use these scripts to respond to the varied discourse styles and instructional demands of teachers and other communication partners. Through the use of scripts, children acquire appropriate behaviors for learning.[40] "In school, language becomes both the object of knowledge and the means through which knowledge is acquired. Thus, within the early school years, and beyond fourth grade in particular, the role of language becomes almost inextricably intertwined with executive functioning and the self-regulatory process" (p. 267).[36] In this conceptual framework, language skills form a base for development of executive functioning and self-regulation and become an integral part of those functions.

Several authors[40–44] have recently provided research that points out the connection of social communication to learning, community participation, and acceptance. The following concepts were suggested:

1. Social communication is a precursor to successful communication in school.
2. Poor social skills include inability to maintain eye contact; lack of recognition of nonverbals, such as reading facial expressions and knowing when a person is too close in personal space; inability to comply with the rules of conversational turn-taking; disruption of conversation with irrelevant topic changes; and inability to recognize when hurtful or unacceptable comments have been made.
3. Strategic learning (ability to find generalizations and main ideas rather than memorizing specific details) is important to successful learning in all individuals. Students with TBI often lack strategic learning skills. They are unable to surmise the gist of a message and, often, cannot locate the main idea when new concepts are presented at school.
4. Ability to employ strategic learning and development of social communication is as significant as emphasis on academic learning in a school environment.
5. Provision for teaching strategic learning/gist concepts and attention to social communication abilities is essential to successful learning.

Addition of these concepts to individualized education plans (IEPs) and other academic modifications should be considered.

Challenges to language, executive functioning, social communication, and self-regulation for a child with cognitive–communicative problems

When a student with TBI is faced with learning and behaving challenges, teachers and therapists should appreciate the part that language plays in the development of executive functioning skills that can lead to increased self-monitoring. The student with cognitive–communicative problems will be at risk in any learning situation and will also have problems with the development of executive functioning and self-regulation skills. Teachers and therapists will often try to modify behaviors in the classroom without first assessing and intervening with language-based learning that includes strategic and gist learning and social communication. Thinking about development and treatment from Singer and Bashir's[36] framework may be beneficial when developing plans for educational intervention.

Cognitive–communicative problems can be directly related to problems with curricular-based knowledge and skills areas. Each grade level has published curricula that guide teachers in knowing what should be achieved during the academic year. The relationship of language demands

on the curriculum and the effect on a child with TBI is outlined in Figure 34.4. (The information in this figure is intended to provide an idea of what the curriculum demands could be and is not intended to be all-inclusive.) By obtaining the curriculum for a specific grade level and reading through the knowledge and skills expected, a therapist or teacher should be able to anticipate the challenges to the student with TBI and propose teaching modifications that account for the learning challenges of the student.

Challenges to learning after concussion

Ashley has considered concussion elsewhere in this text (see Chapter 19). Thus, the mechanism and acute care concerns are not addressed in this chapter. It is important to

The student will often face challenges with language skills within the curriculum. Following are examples of the demands and possible interventions.

ENGLISH AND LANGUAGE ARTS

Language demands on curriculum	Challenges to student with TBI	Possible proactive solutions
1. Interpret "wh" questions in spoken and written form.	1. Lack of problem solving skills to sort out different meanings of key words to aid in answering "wh" questions.	1. Teach main idea of "wh" questions (who means person, what means fact, etc.).
2. Process grammatical structures, sometimes rapidly.	2. Slowed information processing—unable to sort rapidly; inability to learn new grammatical structures and use functionally.	2. Give information at slower pace; review grammatical structures and help to use functionally in spoken and written output.
3. Understand abstract word meanings (antonyms and synonyms).	3. Difficulty knowing similarities and differences.	3. Teach similarities and differences and how to recognize in spoken and written materials.
4. Employ accurate recall and use of retrieval for word meanings and facts.	4. Short-and long-term memory problems.	4. Encourage vocabulary development within specific curriculum areas by use of memory devices, such as notebooks, associations, and categorization.
Add specific language demands for your client.	**List possible problem areas.**	**Suggest interventions for the therapist and teacher.**

SOCIAL STUDIES (HISTORY AND GEOGRAPHY)

Language Demands on curriculum	Challenges to student with TBI	Possible proactive solutions
1. Employ temporal terms, concepts, and relationships.	1. Difficulty with episodic and temporal events.	1. Use compensatory strategies for episodic memory.
2. Knowledge of past, present, and future.	2. Unsure of relationships that include time plus space.	2. Teach concepts of time and make relationships functional.
3. Use of organizational and sequencing abilities.	3. Poor development of executive functioning.	3. Supply compensatory strategies for sequencing and organization.
4. Ability to take notes from lecture, identify main ideas and supporting information.	4. Inability to locate main ideas and lack of recognition of supporting data.	4. Teach main idea versus supporting data.
5. Ability to recall and retrieve related information.	5. Memory impairments for recall.	5. Develop compensatory strategies for recall and retrieval.
Add specific language demands for your client.	**List possible problem areas.**	**Suggest interventions for the therapist and teacher.**

Figure 34.4 Language demands on the curriculum. Implications for the student with TBI. (From Blosser, J. and DePompei, R., *Pediatric Traumatic Brain Injury: Proactive Interventions*, 2nd ed., Delmar, New York, 2003, pp. 298–301. With permission.) (*Continued*)

MATHEMATICS

Language demands on curriculum	Challenges to student with TBI	Possible proactive solutions
1. Ability to use syntactic and semantic components of language to solve verbal math problems.	1. Difficulty with semantic aspects of word problems.	1. Aid in finding the main idea of the verbal math problem—what information is needed to solve the problem.
2. Recall and use "math language" when needed—many complex concepts are carried in a few words: "divide," "multiply," "add."	2. Unable to recall the concept associated with a single word, misses the instruction to "add."	2. Teach the meaning of single words that carry considerable intent—aid in recall of the concepts and processes underlying the single word.
3. Employ sequencing skills to complete a process.	3. Sequencing skills are often impaired.	3. Work on meaningful, functional sequencing skills.
4. Use language to understand the word problem and then complete the math to solve the problem.	4. Poor recall, inability to find relevance within the word problem. (oftentimes, the child with TBI can do the math if he/she can understand the words that formulate the problem.)	4. Develop ability to find the main question within the problem and associate the concepts necessary to solve it.
Add specific language demands for your client.	**List possible problem areas.**	**Suggest interventions for the therapist and teacher.**

SCIENCE

Language demands on curriculum	Challenges to student with TBI	Possible proactive solutions
1. Knowledge of concepts such as more than/less than, when/then, before/after.	1. Inability to recognize relationships and concepts that are not concrete in nature.	1. Teach relationships within the word pairs.
2. Recognition of cause and effect.	2. Inability to recognize relevance of cause and effects.	2. Aid in recognizing the relevance of cause and effect.
3. Recall of specific terms and processes.	3. Vocabulary development may be sporadic and inability to recall newly learned words is problematic.	3. Devise memory strategies and compensatory aids for new vocabulary.
4. Demonstration of learned knowledge in projects that often require sequencing of events and steps.	4. Problems sequencing.	4. Employ memory aids for sequencing multiple steps (including written cues).
Add specific language demands for your client.	**List possible problem areas.**	**Suggest interventions for the therapist and teacher.**

Figure 34.4 (Continued) Language demands on the curriculum. Implications for the student with TBI. (From Blosser, J. and DePompei, R., *Pediatric Traumatic Brain Injury: Proactive Interventions*, 2nd ed., Delmar, New York, 2003, pp. 298–301. With permission.)

know that in youths, concussions are serious, and many occur without a loss of consciousness.[45–47] Many concussions clear without intervention, but most require periods of time for rest and intervention for best recovery. It is difficult to identify which students will clear without intervention. Therefore, where children and adolescents are concerned, the concepts of returning to school after a concussion and returning to learning[48] are key concepts to consider. Recognize that some students will need modifications for only a short while, and others, who experience a longer recovery time, will need written modifications in a Section 504 plan.

It is important to be able to recognize the challenges to learning after a concussion and to enact proactive solutions to assist the student during the time of concussion. There are many websites (see listing at end of chapter) that provide complete information about signs and symptoms, classroom modifications, and teacher and parental guides

Table 34.2 Concussion implications for the classroom

Area of concern after concussion	Possible classroom behavior that indicates difficulty	Proactive solution for student
Cognitive–communication	Unable to concentrate	Provide information in smaller chunks
	Forgetting recently learned information, conversations, or assignments	Allow for written and verbal cues; use note-taker or provide written notes for reference
	Slow to process information (verbally or written)	Allow additional time for response; provide alternative methods for test-taking
	Asks for repeats	Provide written and verbal cues and notes
	Word finding/naming (vocabulary) difficulty	Preteach new vocabulary; cue using categorization and association
	Poor social interactions with others (easy to anger, rude, interrupts with irrelevant information)	Do not punish unacceptable behaviors; work on social skills one on one
	Confused about recent activities or experiences	Use technology (tablets, smartphones) to record cues as activities occur; use day organizer for reference
	Unable to attend to task completion	Break tasks into smaller pieces so each portion is successfully completed
Physical	Headaches in school	Allow for rest breaks
	Dizziness	Provide calm environment without multiple distractions
	Fatigue: Sleeping more or less than usual	Allow for rest breaks; plan daily schedule with variety of difficult then less difficult classes interspersed
	Vision problems with sensitivity to lights	Avoid fluorescent lights when possible; decrease brightness on computers, smartphones, tablets; limit time on computers; electronic gaming devices
	Hearing issues with noise (gyms, concerts, music causing irritability)	Avoid loud activities, including gym classes
Emotional/behavioral	More irritable in the classroom	Provide clear schedule for the day; recognize beginning of irritable behavior and provide alternative activity
	Feeling anxious or tense	Provide time for rest during the day; provide clear schedule of activities for the day
	Feeling depressed	Point out strengths and successes during each day
	Easily overwhelmed by school requirements or activities	Diminish schedule to reasonable load that can be successfully accomplished; add activities only when success is demonstrated; decrease or eliminate homework

for return to learn. The chart in Table 34.2 is a short list of challenges to learning and possible proactive classroom solutions.

All states have enacted concussion laws for young athletes. The laws vary from state to state, but all include the following requirements:

1. Athletes, their parents, and coaches must receive information about concussion, including how to recognize symptoms.
2. If a concussion is suspected, the athlete must be removed from play.
3. Written authorization for return to play from a medical professional (defined differently in each state) trained in the diagnosis and management of concussion.

It is essential to recognize that children other than athletes can sustain concussions, and these young people also should have the same protocol for returning to daily functioning. Most importantly, all students should be prepared for return to learn. There are a number of websites that contain complete information regarding concussion, symptoms, and information for school return. See reference section for a listing.

TREATMENT OF COGNITIVE–COMMUNICATIVE STRENGTHS AND NEEDS: AN INTEGRATIVE APPROACH FOR SCHOOLS

An integrated approach to treatment assumes that the student is assessed and interventions are provided in an

ongoing manner. Cognitive–communicative and behavioral deficits following TBI will require special assessment and intervention throughout the student's education. Although long-term deficits following TBI are well documented, empirical research on the effectiveness of particular instructional practices for dealing with subsequent learning problems in students with TBI is lacking.[49–54]

Given this absence of research, Ylvisaker et al.[51] stated that teachers must examine effective teaching practices and proven instructional interventions for students with other types of learning difficulties. They recommended identifying students by functional need and connecting identified needs with research-based strategies.

Identifying student needs

Determining the individual needs of a student will require careful evaluation of the student's functioning. To obtain a comprehensive picture of the student's functioning, assessment information from a variety of sources (e.g., neuropsychology, speech–language pathology, occupational therapy) should be combined with functional evaluation of the child's skills. The child's performance and needs in the following areas should be taken into consideration during the evaluation: motor, sensory (i.e., vision and hearing), health, social/emotional, cognitive, speech and language, and academic.

For the child with TBI, multiple physical factors may influence how he or she performs in the classroom, especially in the first year following the injury, and a thorough review of the child's medical records should be included as part of any comprehensive assessment. As a result of a TBI, children may have significant motor sequelae, including ataxia, muscle weakness, tremors, rigidity, or spasticity, and deficits in balance and coordination. Impaired motor speed and coordination may influence performance on timed tests and daily tasks. Tremors or incoordination may make it difficult for the child to copy, draw, or perform manipulative tasks and to negotiate stairs and crowded hallways. Vision and hearing can both be affected by TBI. Visual problems may include blurred or double vision, problems of visual pursuit, extraocular movements, or visual field defects. Hearing loss after TBI most commonly results from a fracture of the temporal bone with transverse fractures resulting in sensorineural hearing loss and longitudinal fractures involving the middle ear structures associated with conductive hearing loss.[55] Sensory problems may require referrals to pediatric audiologists or ophthalmologists for any children who are displaying behaviors suggestive of hearing or visual impairments. Even if the child has made good physical recovery, reduced stamina and fatigue may continue to plague the student for months after the injury. Medications prescribed to control or prevent seizures or medications to manage muscle tone or function may have side effects that affect performance and should be monitored for their intended and nonintended consequences. Chronic pain from headaches or orthopedic injuries sustained at the time of the child's TBI can negatively impact day-to-day functioning.

Language and social pragmatic skills of the student with TBI are often compromised after the injury. Attention to all aspects of the previously outlined challenges are to be considered when planning for student reintegration to school and community. How these cognitive–communicative language-based issues will impact both social/emotional and academic learning must be carefully considered when determining the overall functioning potential.

Case of John (continued)

John was evaluated and found to have the following curricular-based learning challenges:

Language Arts: Vocabulary development essentially stopped after first grade. He demonstrated word-finding problems and fluency difficulties that were based in his lack of ability to express himself verbally. The following dialog is a language example of John's discussion about his need for a computer.

Therapist: "Is there anything else that would help you?"

John: "Yeah, to have my old own special *thing* (gestures typing) so I, I, I, um, can work all, all of my, my, um, assignments on one *thing* because of what I'm to a sharing a bunch of *things* with a bunch of other students and I cannot do that."

Therapist: "Books? Like your books in class? Is that what you are sharing?"

John: "No, no! My, ah, own own, ah *laptop computer*. See once first I use one *thing*, ev, ever, everybody else wan to use it."

The same word-finding problems were also reflected in spelling and writing attempts. His reading and spelling were found to be at the second grade, third month level. Writing was at kindergarten, nine month level. He used gestures well and was often assumed to be communicating better than his language capacity indicated he could.

History: John was unable to understand concepts of time and place and could not deal with "when" questions. He could not sequence temporal events and experienced difficulty with most history-based concepts.

Science: John had no concepts for sequencing beyond two steps. He was unable to use deductive reasoning and saw no cause–effect relationships.

Math: John was able to complete most addition, subtraction, multiplication, and division problems. He could not apply the math skills to word problems.

Evaluation of actual task performance in settings in which the student's adaptive skills are called into play is critical because assessments given under ideal conditions do not reflect the kind of difficulty a student may face in a busy classroom with less guidance and structure. Ongoing functional assessment of the student in the school environment is required to accurately determine the student's current functioning and needs in order to develop interventions.

The following section discusses two methods for functional interventions. First, suggestions for addressing underlying cognitive processes in the classroom are presented. This is followed by a discussion of teaching techniques that may aid the acquisition of academic skills. It is hoped that use of these strategies will establish outcomes for the student that develop independence for learning and generalization of what was learned to new situations.

Strategies for addressing underlying cognitive processes

Results of the comprehensive evaluation may reveal that the student has a number of specific deficits in underlying cognitive processes. To determine which teaching methods may be most effective in meeting an individual student's particular needs, educators need to examine instructional interventions and teaching practices that have been proven effective for addressing similar deficits in students with other types of learning difficulties. For example, organizational impairments following TBI will necessitate proven instructional strategies for organization, such as task analysis (breaking a given task into components or steps) and advanced organizational support (providing an oral or written preview of information to be covered in a lesson). Lack of strategic learning ability will require specific strategy instruction, such as the teaching of word identification strategies, paragraph-writing strategies, test-taking strategies, etc. (see Deshler et al.[56] for a comprehensive review of strategy research and methods). Weak executive function skills will call for instruction in self-regulation procedures (e.g., goal setting, self-monitoring).[57] Additionally, a variety of effective teaching practices that have been found to be correlated positively with student achievement (e.g., the provision of structured lessons, guided practice, immediate feedback, clearly stated expectations, frequent review, and small-group instruction) may be particularly beneficial for meeting the needs of students with TBI.[49]

In conjunction with matching specific teaching methods to identified needs, a number of teaching strategies and accommodations should also be considered to address problem areas. These strategies can be successfully employed in general education settings or in the context of special education environments. A sampling of common deficits following TBI is identified here, followed by examples from the comprehensive lists of teaching strategies for students with brain injuries by Tyler et al.[50] and Tyler and Mira.[57] Additional recommendations can be found at websites listed in the resource section provided at the end of this chapter.

ATTENTION/CONCENTRATION

To improve attention and concentration, educators should do the following:

- Reduce distractions in the student's work area (remove extra pencils, books, and so on)
- Provide preferential seating (an area that has the least amount of distraction and is closest to where instruction is taking place)
- Divide work into small sections and have the student complete one section at a time
- Establish a nonverbal cueing system (e.g., eye contact, touch) to remind the student to pay attention

MEMORY

To aid memory, educators should do the following:

- Teach the student to use external aids, such as notes; timers; calendars; electronic organizers, such as personal data assistants or smartphones; and assignment books as self-reminders to compensate for memory problems
- Frequently repeat and summarize key information
- Use visual imagery, when possible, to supplement oral content
- Teach the student to categorize or "chunk" information
- Relate new information to the student's relevant prior knowledge
- Demonstrate techniques, such as mental rehearsal and use of special words or examples, as reminders
- Ask the student to rehearse and summarize information verbally

ORGANIZATION

To improve organization, educators should do the following:

- Provide the student with written checklists of steps for complex tasks
- Color-code the student's materials for each class (textbook, notebook, supplies)
- Provide an assigned person to review the schedule at the start of the school day and organize materials for each class
- Supply outlines coordinated to class lectures (require the student to take notes within each section)
- Teach the student to use a personal data assistant, smartphone, or tablet to organize the day

DECREASED SPEED OF PROCESSING

To help the student compensate for decreased speed of processing, the educator should do the following:

- Deliver instruction in small increments
- Allow the student to have additional time to process information and complete tasks

- Provide sufficient time for the student to respond to verbal questioning
- Pair verbal instructions with written instructions
- Allow the student to take exams in settings that do not have time restraints

PROBLEM SOLVING

To help the student to develop problem-solving skills, the educator should do the following:

- Have the student generate possible solutions to problems as they arise during an activity
- Teach the student the steps involved in problem solving (e.g., identify problem, list relevant information, evaluate possible solutions, create an action plan)

REDUCED STAMINA/FATIGUE

To help the student to cope with chronic fatigue and reduced stamina, the educator should do the following:

- Provide student with regularly scheduled brief in-class or out-of-class rest breaks
- Break down assignments into small segments that can be completed in short periods of time
- Allow extra time to complete assignments

MOTOR DEFICITS

To help the student to cope with motor deficits, the educator should do the following:

- Allow the student extra time to pass between classes (have the student leave class early to avoid crowded hallways)
- Enlist classmates to help student carry lunch tray
- Facilitate computer use through adaptations (oversized keyboards, key guards, voice-activated programs, word prediction programs, etc.)

SENSORY DEFICITS

To help the student to cope with sensory deficits, the educator should do the following:

- Provide preferential seating
- Consult with an occupational therapist about possible modifications in the classroom
- Provide large-print books or audio books, depending on student need
- Position materials within the student's best visual field

Addressing academic deficits

A student may require specialized assistance or accommodations to continue to participate in the regular curriculum following a TBI. A number of adaptations that will increase the success of student learning can be provided during the teaching of academic subject matter. Tyler et al.[50] provided the following examples of suggested techniques for addressing underlying deficits while teaching subject matter.

MATH

Educators should do the following:

- Demonstrate mathematical concepts using concrete items and allow the student to use manipulative items to solve math problems
- Create functional activities for the student to practice mathematical concepts (e.g., planning a budget, purchasing small items from a school store)
- Practice word problems with pictures or stories that relate personally to the student
- Allow the student to use a calculator to aid in solving multiple-step problems

READING

Educators should do the following:

- Review key vocabulary words prior to reading material
- Highlight key words with a colored marker
- Provide the student with key questions to answer before reading
- Ask the student to orally summarize content after reading small segments of a large passage

WRITING

Educators should do the following:

- Provide for alternative response modes for work (e.g., let the student dictate responses, audio record answers)
- Allow the student to take exams orally
- Provide specialized writing paper (e.g., raised lines)

In some cases following TBI, a student may no longer be able to acquire information and skills using traditional methodologies and curriculum provided in the general education settings even with accommodations. In such cases, a specialized intensive instructional approach is required. One such specialized approach—direct instruction (DI)—was identified by Glang et al.[58] as an evidence-based instructional model that shows particular promise for students with TBI because it combines "systematic analysis and design of content and careful instructional delivery for attacking complex academic content and mastering critical basic academic skills" (p. 246).

Using the DI model, carefully designed curriculum materials are delivered in a highly structured, systematic, instructional manner that incorporates several teaching practices that have been consistently linked to pupil achievement outcomes (see Adams and Engleman[59] for a comprehensive description of the model and summary of research). Educators can apply the DI model to existing curriculum or use one of the readily available commercially published DI materials for teaching reading, mathematics, and spelling.

There is significant evidence supporting the use of DI with many populations of children, with and without

disabilities, and in preliminary studies. DI techniques have been shown to be effective in teaching both academic and behavioral skills to children with brain injuries.[60] Glang et al.[60] stated the DI model is thought to be effective with children with brain injury because it specifically addresses many of the common learning problems typical of these students. For example, DI provides rapid instructional pacing and high levels of student engagement that address attention and concentration difficulties. The model also provides sufficient practice of skills, teaches generalizable strategies, and delivers corrective feedback to address difficulties students with brain injury face in learning new concepts and information.

Assessing teaching strategies

The effectiveness of these practices must be continually evaluated once instructional practices are employed. Also, because of the rapidly changing needs of the student following TBI, ongoing functional assessment of the student in the school environment is required to determine if the student is currently functioning accurately.

Case of John (continued)

The IEP team developed an educational program to meet John's unique learning needs based on results of the comprehensive evaluation and functional assessments. John received specialized instruction in reading and language arts. John's special education teacher used commercially developed DI reading and spelling materials, which provided the structure, practice, and immediate feedback John needed to succeed. The special education teacher provided support for John in his regular education history, science, and math classes. John was able to participate in the general education curriculum with assistance with developing timelines and sequencing information, providing visual–spatial displays, and preteaching content vocabulary. Special accommodations, such as reduced writing requirements, preferential seating, and peer assistance were provided throughout the day. John also received school-based speech–language services for 30 minutes, three times per week. During this time, John's word-finding problems were addressed. The decision to stimulate language and not work directly with the fluency problem was based on the thought that, with increased expressive competence, fluency patterns of repetition and word substitution would decrease. Shortly after the IEP was implemented, John began showing progress. John's family and teachers reported that, in addition to making academic gains, John's emotional well-being had also improved since he had begun receiving the help he needed.

LAWS AND REGULATIONS THAT AFFECT EDUCATION, PROVISION OF SERVICES, AND TRANSITION FOR STUDENTS WITH TBI

Students with TBI may require special education services, special assistance, or accommodations because of long-term physical, cognitive, language, and psychosocial difficulties. Students can access such services under the Individuals with Disabilities Education Act (IDEA) or Section 504 of the Rehabilitation Act.

IDEA

IDEA, an outgrowth of the Education for All Handicapped Children Act of 1975 (P.L. 94-142), guarantees a free appropriate public education for children 3 to 21 years old. To receive services under IDEA, a multidisciplinary team must evaluate and determine a student to have a qualifying condition that requires special education services. Since 1990, IDEA has recognized TBI as one of the categories that qualify students for special education services. The IDEA regulations[61] define TBI as follows:

> …an acquired injury to the brain caused by an external physical force, resulting in total or partial functional disability or psychosocial impairment, or both, that adversely affects a child's educational performance. [TBI] applies to open or closed head injuries resulting in impairments in one or more areas, such as cognition; language; memory; attention; reasoning; abstract thinking; judgment; problem-solving; sensory, perceptual, and motor abilities; psychosocial behavior; physical functions; information processing; and speech. [TBI] does not apply to brain injuries that are congenital or degenerative, or to brain injuries induced by birth trauma. (§300.8[c][12])

Although most states adhere to the federal definition of TBI, each individual state's TBI definitions and determinations of eligibility do vary. A state's TBI definition can be accessed through its State Department of Education website. For a state-by-state summary of how TBI is defined by law, see Vaughn.[62]

An IEP must be devised and carried out once the team has determined a student is eligible for special education. The IEP is, essentially, a document that describes the action plan for the student's educational program and serves as a contract between parents and the school for the delivery of educational services to the student.

A full continuum of special education placement options, ranging from homebound services to placement in the general education classroom with special education support, is available through IDEA. Regardless of setting, the term *special education* means specially designed instruction to meet the unique needs of the student and may include

direct skills instruction, the teaching of compensatory strategies, and vocational education as well as the provision of modifications and accommodations. Related services, such as speech–language therapy, occupational therapy, physical therapy, counseling, adaptive physical education, behavior management services, audiology services, recreation therapy, social work services, school health services, parent counseling and training, and transportation are also available through IDEA. According to IDEA, children can receive these services if they are deemed "educationally relevant;" however, how individual districts interpret educational relevance is often open to debate.[63] Glang et al.[63] reported many students transitioning from hospital or rehabilitation settings to school initially receive a combination of educationally based therapy at school and medically based outpatient rehabilitation therapy paid for by insurance providers or Medicaid.

According to Tyler and Savage,[64] IEPs written for students with TBI require procedures that vary from traditional IEP development because of the underlying medical cause of the disability, the resulting deficits, and the evolving needs of the child. For example, information from a variety of sources and disciplines outside the school system needs to be translated to determine present levels of functioning. Goals need to address cognitive processes rather than strictly academic impairments, and IEP reviews need to be conducted more frequently (e.g., every 2 to 3 months, initially) to address dramatically changing needs. In addition, the student's initial IEP should be a joint venture among the health care facility, the school, and the family.

Section 504

Not all students need, or are eligible for, special education even though a brain injury may affect learning. A student may still be able to participate in the general education program by receiving services under Section 504 of the Rehabilitation Act of 1973 with classroom adjustments and curriculum modifications. Section 504 is a civil rights act that protects the civil and constitutional rights of persons with disabilities. Schools receiving federal financial assistance may not discriminate against individuals with disabilities, according to Section 504. Classroom teachers and school staff are required to provide for them because some students with disabilities may need adjustments or modifications to benefit from their educational program. Unlike IDEA, Section 504 is a regular education management responsibility.

A person must be considered disabled to receive services under Section 504. A person may be considered disabled if the individual 1) has a mental or physical impairment that substantially limits one or more major life activities (e.g., walking, breathing, learning, working), 2) has a record of such an impairment, or 3) is regarded as having such an impairment. A student must be evaluated by a team of individuals who are familiar with the student to determine eligibility for Section 504. The evaluation typically consists only of gathering documented information from a variety of sources, and because most students with TBI have documentation from outside sources, additional evaluation may not be required. The team then reviews the evaluation data to determine the nature of the disability and how it affects the student's education.

A Section 504 plan describing services or accommodations is developed by the team to document services. The plan lists specific adjustments to the learning environment and modifications to the curriculum. The plan also indicates who is responsible for carrying out and evaluating each adjustment or modification. Any number of accommodations can be provided with a 504 plan based on the student's needs. They include environmental, curriculum, methodology, organizational, behavioral, and presentation strategies. Tyler and Wilkerson[65] offer information about accommodations that may be provided through a Section 504 plan. Table 34.3 provides a sampling of their suggestions for possible accommodations to meet common concerns following brain injury.

Section 504 should be considered as a venue for receiving needed support for students who do not qualify for services under IDEA because Section 504 protections extend to a larger population of students than IDEA. In addition,

Table 34.3 Section 504 plan accommodation

Consider the following accommodations for students qualifying for 504 services:
Memory deficits
Written as well as verbal direction for tasks
Frequent review of information
Monitored planner (check-off system)
Fatigue
Reduced schedule
Planned rest break
Fine motor difficulties
NoteTaker for lectures
Oral examinations
Scribe for essays
Processing delays
Increased time to complete assignments or tests
Extended time to provide verbal answers
Complex directions broken into steps
Attention
Visual and/or verbal prompts
Preferential seating (away from distracting areas of the classroom—often in the middle of the classroom beside a well-organized student)
Technology
Computer/word processor for responding and homework
Use of communication devices

Source: Tyler, J. and Wilkerson, L. R., *Section 504 plan checklist for a student with a brain injury*, Lash and Associates Publishing/Training, 100 Boardwalk Drive, Suite 150, Youngsville, NC 27596, USA. Used with permission.

because IDEA does not apply to students who have graduated from high school or those who have reached age 22, Section 504 serves as the vehicle for obtaining services in postsecondary settings.

Zirkel and Brown[68] recommend initially meeting the student's concussion-related safety and learning needs via either an individual health plan or, depending on state laws and local policy, professional due diligence alone by providing "generous academic adjustments" in the case of students diagnosed with concussion because the majority of concussions typically resolve within the first weeks after the child returns to school.[66,67] However, for 10% to 20% of students, the symptoms of concussion persist for a number of weeks, months, or even years.[67] If the student's symptoms have not resolved in the typical time frame, a more individualized and targeted approach, such as a Section 504 plan or special education services, will be required.[68,48] More information on when to write a Section 504 plan for students with concussion can be found at http://www.getschooledonconcussions.com/.

TRANSITIONING STUDENTS WITH TBI

Transitioning is often thought of as a one-step activity of moving a child from the hospital to the school following a TBI. Although the importance of careful planning for school reintegration has been well documented in the literature,[2,21,32,51] there are a number of other important transitions that occur throughout a student's education career. Transitioning occurs repeatedly over the lifetime of the student with TBI in reality. Certainly, the student will transition from medical interventions to home, school, and community. The child will encounter transitions with the passage from grade level to grade level, the change from elementary to middle school, and middle to high school once in school. Beyond that, the student will transition from high school to postsecondary education, employment, and community living. Specialized planning for all of these transition points is required because each can present formidable challenges for students with TBIs, resulting from cognitive and behavioral impairments that make it difficult for the students to adjust to changes in environments, routines, and expectations.[58]

Hospital-to-school transition

The transition from a hospital or rehabilitation setting to school is the first critical point in securing appropriate educational services for the student with TBI. Strong interprofessional collaboration among parents, health care providers, and educators is recommended[69] with communication beginning as soon as the student is hospitalized.[51] Research has shown that, although informing educators that a student has been treated for a TBI does not guarantee the child will receive appropriate services, failing to inform school personnel about the student's TBI significantly decreases the likelihood that educational services will be provided or tailored to the student's specific needs.[54] Hospitals and rehabilitation centers should have an established protocol in place for ensuring medical staff obtain appropriate releases from parents, school systems are notified, and the transition process is carried out for all students treated for TBI.

In-school transitions

Do not assume the plan or information is being transferred from teacher to teacher, supervisor to supervisor, or school to school as the student transitions from setting to setting. Annual reviews of progress and modifications of plans are essential to continued success.

It is also crucial that the plan be shared with all individuals who interact with the student at work, school, or in the community whenever there is a change in personnel or location throughout the year. Help parents develop a notebook of personal information related to their child (e.g., medical records, IEP/504, work samples, etc.) that they can share with a variety of agencies as they advocate during transitions. A checklist for transitioning is depicted in Figure 34.5.

Postsecondary transition

Postsecondary outcomes are poor, with research showing that young adults with TBI who received special education services in high school are employed and enrolled in postsecondary education at lower rates than peers in the general population, for many students with TBI.[70,71] Although this is certainly discouraging, there may be modifiable variables that can affect postsecondary outcomes. For example, Todis and Glang's[72] longitudinal study showed students with TBI who received transition services that linked them with disability services and support agencies were more likely to complete postsecondary programs, thus underscoring the importance of high school transition services.

IDEA requires that a transition plan for movement out of school to postschool activities, employment, independent living, and community participation is included in the student's IEP, beginning at age 16. Specific outcomes must be identified and supported by transition services, which may include academic support, community-based education focused on employment, functional and independent living skills, personal and social content, and career awareness, based on students' needs, preferences, and interests. Planning for any transition must be completed with as much proactive planning and anticipation of challenges as the IEP process requires because the same cognitive–communicative challenges exist for all transitions.

All members of the team should be prepared in advance of the meeting. Some questions that the student and family should think about prior to the meeting include the following:

- What type of education is desired? Regular education, special education services, trade school, 2-year college, 4-year college, none?
- What vocational tracks may be of interest?
- What type of independent living might be desired?

1. Identify key players at each agency.		
2. Determine what policies and procedures exist for all agencies involved.		
3. Provide all pertinent information about the student, including tests, cognitive challenges, behaviors that can be anticipated.		
a. Obtain all written records.		
b. Generate a profile of student strengths and challenges.		
c. Identify the challenges that may interfere with the successful performance of the student.		
d. Provide samples of present work levels that represent capabilities and levels of performance.		
4. Relate the challenges and strengths to the new setting.		
a. Discuss accommodations needed.		
b. Offer choices based on the demands of the setting and the needs of the student.		
5. Determine the agency's readiness to accommodate the student.		
a. Provide adequate staff training.		
b. Assess environment for necessary changes to accommodate physical, cognitive needs.		
6. Determine what assessments may be needed for placement in the agency.		
7. Outline strategies for supporting performance.		
8. Determine which placement, personnel can best meet student needs.		
9. Observe the environment to determine any supports not in place or additional strategies that can help.		
10. Maintain ongoing communication of all involved parties after that plan is begun.		
11. Modify the plan as often as indicated and PRIOR to a serious problem emerging.		
12. Outline a plan of action if problems emerge so staff can be proactive, rather than reactive.		
13. Outline a functional evaluation plan to determine what is working and what should be changed.		
14. Maintain contact among the key personnel identified in Step 1.		
15. Add any other steps pertinent to this student.		

Figure 34.5 Transition planning guide.

- What leisure activities are of interest?
- What are the student's hopes and dreams for the future?
- What strengths does this student have to achieve any of the above desires?
- What challenges to achieving the above goals might exist?
- How can a specific plan be devised to address these challenges in the next few years?
- Who will need to participate in order to work toward these goals?
- What environmental supports or modifications will be needed to facilitate success?
- What evaluation tools will be used to determine whether there is movement toward achieving these goals?

- Who will participate with the student to determine if the goals are being met or if they should be altered?
- How often will a reassessment of this plan be completed?

RESOURCES

- What community resources might be available? For example, the Disabilities Support Services office located on every state college or university campus, Bureau of Vocational Rehabilitation Services (Rehabilitation Services Commission), work–study programs at high school, or volunteer opportunities in the community may be useful.
- What other agencies might be able to help—Drug and Alcohol Boards, YMCA, Medicare, Departments of Mental Health or Mental Retardation/Developmental Delay, Family Services, or Independent Living Centers?
- What opportunities for transportation, housing, and personal assistance might exist through agencies, churches, and social or private organization?

STRATEGIES

- What cognitive challenges may need to be accommodated and how will these behaviors appear in the classroom, workplace, or community?
- What accommodations might work (such as planners, coaches, reminders, adapted equipment, reduced schedules, technology applications for accommodation, note-takers, communication devices)?
- Who should be involved in ensuring these accommodations are provided and are ongoing in support of the student?

In addition, websites have been developed to aid individuals and families in advocating for educational and community living needs (see website listing at end of chapter). Refer to these sources for an in-depth discussion of these areas.

Case of John (continued)

When John was 14, the checklist was employed to establish a transition plan for him. The planning team consisted of John, his grandmother (legal guardian), the director of special education, two classroom teachers, the work–study coordinator, the speech–language pathologist, a representative of the Rehabilitation Services Commission, and a representative of a local rehabilitation center that held a grant to effect school-to-work transition for youth with disabilities.

The original plan included assessing John for his vocational interests as well as discussion about his challenges in academic and social areas. His strengths included fine motor coordination, outgoing personality, math computation, use of gestures to augment communication attempts, and mechanical aptitude.

John was placed in regular classes that emphasized managing skills for daily independent living, home economics, art, and math. He was placed in an LD classroom for assistance with language arts. He began in a vocational school where he learned auto mechanics. He had a job coach with him for all new classes. He attended the local rehabilitation facility 2 days a week where he was taught additional job skills, which included socialization skills training, assistance with strategies for following directions, and self-advocacy training. He called periodic meetings of his IEP and transition teams to discuss progress and additional challenges. Accommodations were made, at his request, for training for job personnel about his poor organization, and he provided an in-service regarding his communication challenges and how he adapted to them. Over the following 3 years, adaptations to his transition plan were completed six times. Training of personnel regarding John's strengths and needs was completed four times as situations in teaching, coaching, and employment changed.

Currently, John is employed half days at a local car dealership, where he is apprenticing as an auto mechanic. He continues his academic work for the other half day where he attends two regular classes and continues with the assistance of the LD teacher. He continues to be challenged academically in language arts. He should graduate this spring at age 19, and the car dealership anticipates hiring him into a full paying position.

SUMMARY

This chapter has focused on the cognitive–communicative challenge that can emerge after TBI. These challenges often are overlooked in the struggle to provide adequate educational programming. When strategies are used consistently and personnel collaborate to provide ongoing transition and intervention, students can modify behaviors and become contributing adult members of society. These plans can be modified for youth with many levels of severity. Although all will not transition to gainful employment, college, or independent living, it is our belief that all can be accommodated into society for a better quality of life. Hippocrates suggested long ago that we use our skills for those who are mildly injured and also for those who are severely injured—that they all deserve our attention and efforts. We think he is right.

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WEBSITES FOR TBI INFORMATION

- Brainline for Kids
  - http://www.brainline.org/landing_pages/features/blkids.html
- Center on Brain Injury Research and Training
  - http://cbirt.org/tbi-education/about-tbi/
- Defense and Veterans Brain Injury Center
  - https://dvbic.dcoe.mil/resources/browse
- LEARNet
  - http://www.projectlearnet.org
- National Association of State Head Injury Administrators
  - http://www.nashia.org/Children&Youth.asp

WEBSITES FOR CONCUSSION INFORMATION

- BrainLine.org
  - http://www.brainline.org/content/2012/05/recovery-from-concussion-in-students.html
- Centers for Disease Control and Prevention: Heads Up
  - http://www.cdc.gov/headsup/
- Get Schooled on Concussions: Return to Learn
  - http://www.getschooledonconcussions.com/
- School-wide Concussion Management
  - http://brain101.orcasinc.com/

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Long-term discharge planning in traumatic brain injury rehabilitation

MARK J. ASHLEY AND SUSAN M. ASHLEY

INTRODUCTION

Traumatic brain injury (TBI) has the potential to visit tremendous change upon an individual and, in some cases, devastation to life as it might have been known to the person prior to injury. Although professionals struggle to find better ways to mitigate the effects of brain injury, treatment must ultimately come to an end. When it does, the fruits of the discharge planning process become more or less apparent. Discharge planners face tremendous challenges at all levels of care, not the least of which is developing a firm understanding of the broad impact of brain injury upon the person and family.

In order to be most effective in discharge planning, it is important to understand the impact of TBI on the individual, family, and society. Jennings eloquently summarizes the writings of March et al.[1] as follows:

> "…TBI is a complex nexus of symbols, norms, relationships, both interpersonal and intrapersonal perceptions and negotiated identities, and caregiving activities. TBI brings forth a new character on the social stage. There enters a person with a different set of memories, feelings, capacities, abilities, and needs placed in a family ecosystem where he is at once an intimate and the stranger. His very presence violates boundaries of many different kinds and provides nearly everyone involved with a serious challenge to their repertory of ordinary social skills and responses. Role reversal and role distance become endemic, everyday issues. Women must relearn how to be wives or mothers, and men, husbands or fathers. Children, now sadly perhaps the wiser or more quick-witted, must reconstruct a relationship with a parent. The entire kinship system shakes" (p. 34).[2]

Jennnings goes on to say, "Then, because TBI plays such havoc with what Thomas Hobbes called the 'small morals' of everyday life (the etiquette of cursing, table manners, personal grooming, and the like), the large morals—the human rights and rules of nondiscrimination, dignity, respect, and social justice—that really matter to our humanity become even more crucial than they ordinarily are. TBI tests not so much things like patience (although it does do that), but, more significantly and tellingly, it tests respect, justice, and love" (p. 34).[2] Jennings suggests, "The primary duty of the family with respect to the person with TBI is not so much protection from bodily harm, nor the promotion of best interests, at least as that term is commonly understood. Instead, familial and caregiving duties should revolve around practices needed to sustain the person's human flourishing or quality of life as a person. Providing comfort and safety, mere guardianship, is not enough" (p. 36).[2]

There are a number of practical challenges to discharge planning that bear some comment. First, length of stay (LOS) in medical treatment and rehabilitation has been impacted by huge decrements wrought by health care finance mechanisms such as health insurance. Since 1990, the overall LOS for acute hospitalization and for hospital-based rehabilitation has decreased markedly for persons with TBI.[3,4] Overall, hospitalization rates for TBI decreased by 50% from 1993 to 1996. Kreutzer et al. reported acute care LOS averaged between 22 and 29 days between 1990 and 1994 and decreased to less than 20 days in 1995 and an average of 16 days in 1996. Average LOS for acute rehabilitation hospitalization decreased from 47.74 days in 1990 to 29.49 days in 1996. The authors attributed these changes to concurrently occurring changes in overall delivery of medical services resulting from the impact of managed care. It seems reasonable, nonetheless, to conclude that earlier discharges from shorter LOS are likely to complicate the discharge planner's job. In 2016, LOS for hospital-based treatment of brain injury less than 14 days is not uncommon.

At the same time that societal trends toward lesser treatment increase, discharge planners are left with fewer discharge options and an ever-present need for pragmatism in securing a suitable discharge scenario for a given patient. The process of discharge planning varies with the setting in which it is undertaken, the amount of information that is available to the discharge planner, and resources that may be available for ongoing care for the individual. And, as if the process were not complicated enough, the discharge planner is dealing with a disease that is likely the most complicated in its impact and ramifications for the individual, the family, and society. Additionally, employment retention in most systems of care is quite short. Professionals who undertake discharge planning are less likely to be appropriately familiar with discharge options on a local, regional, or national scale, thereby necessarily impacting the nature of choices provided to patients and their families. Finally, further restrictions imposed by payer networks or payer medical director discretion make discharge planning an immense challenge.

It is also difficult to approach the subject of discharge planning with a single view due to the different levels of treatment from which discharge planning must occur—that is, acute hospitalization, hospital-based rehabilitation, or various postacute rehabilitation settings. Rotondi et al. identified a trend of inconsistent findings in the professional literature regarding the needs of caregivers and persons with injury that resulted in confusion or disparate reporting of needs.[5] These authors undertook a longitudinal data collection process using semistructured interviewing of individuals with injury and their caregivers across four postinjury phases: 1) acute care; 2) inpatient rehabilitation; 3) return home, a transitional period that typically lasted about 3 or 4 months after discharge from inpatient care; and 4) a post–return home phase that could be described as "life in the community." Of greatest interest to the reader are the findings relative to phases three and four pertaining to the longer-term discharge picture. First, there are differences in the reported needs between individuals with injury and their caregivers. This is consistent with other literature in this area and points to the need to consider both individuals with injury and caregivers in treatment formulation. Six themes were identified as important across all phases: 1) understanding injuries, treatments, and consequences; 2) emotional and mental health of persons with TBI; 3) financial assistance; 4) guidance; 5) family emotional and mental health; and 6) finding and evaluating providers. In the longest term phases, additional themes of importance included the following: 1) reassessment of the person with TBI, 2) community integration, 3) support group, 4) support from family and friends, 5) care coordination, 6) respite services, and 7) life planning. These findings point to the needs individuals with injury and their caregivers have for differing types of information, services, and support across time.

Families are not always ready to take in information when professionals are available to provide it. Professionals may provide information and terminology that is too complex to be understood or may provide that information at a time when the family or the individual with injury are unable to understand it. The findings of Rotondi et al.[5] strongly support the need for the development of an easily accessible system of information that is designed to meet the diverse needs of the entire population of individuals living with brain injury and their caregivers as they progress along the continuum from injury to long-term living. Additionally, treaters engaged in the earliest phases are well advised to understand the kind of information that is relevant to the person with injury and their caregivers at points in time at which these early treaters are involved. Knowledge of the long-term information, service, and support needs can be utilized by early treaters to begin to prepare individuals with injury and their caregivers for the longer term. It is unlikely, however, that treaters in the early phases will successfully provide a complete preparation for the long term. For those individuals and/or families who tend toward a desire to quickly terminate treatment in the early phases, perhaps thinking that return home will mean a return to normal functioning, this information may be useful in encouraging them to complete treatment as recommended and better prepare for the longer term. Finally, these findings are particularly pertinent when one considers that the predominant service delivery model is one that is "front-end loaded" with medical and rehabilitative services. The latter two phases are far less impacted by availability of medical and rehabilitative services, resulting in the need for individuals with injury and their caregivers to "go it alone."

Discharge planners frequently must focus on the immediate discharge environment following a treatment setting. Although this is quite important, such an approach does not tend to prepare the person or the caregivers for the longer term. As the field of TBI rehabilitation has matured over the last 25 years, it has become increasingly possible to consider other aspects of outcome. Outcome has traditionally encompassed self-care skills, independent living skills,

and return to work. Although the importance of vocational skills cannot be overstated, there is no dependable or reliable means of securing well-designed vocational rehabilitation services for persons who have sustained TBI. So issues such as caregiver preparation and burden, the impact of catastrophic disability upon family systems and family members, and factors such as life satisfaction and health-related quality of life have emerged as viable concerns in discharge planning as they bear upon the viability and durability of many discharge placements.

The medical model tends to focus upon medical issues with less attention paid to issues of life satisfaction.[6] Regardless of the level of disability following injury and the cessation of treatment, life satisfaction for the injured person and his or her caregivers should be a major consideration of any assessment of outcome. Ultimately, of course, the degree to which sequelae of TBI are resolved during rehabilitation will bear substantially on level of life satisfaction achieved by the injured person.

Because relatively little attention is afforded to the arena of life satisfaction in discharge planning, many of the issues in this chapter bear directly or indirectly on this topic. People survive TBI. The question ought to be how well they and their caregivers survive the immense trauma inflicted by the injury itself and the absolute upheaval of life that often follows. To that end, discharge planners should work to identify not only the next immediate care or treatment setting, but they should also work with their treatment team and community resources to pull together educational materials and resources that will address the issues that are addressed in this chapter. The intent should be to address both the immediate and long-term needs of persons with TBI and their caregivers.

Most discharges from treatment occur as events planned and agreed-upon among all parties. A special circumstance is encountered, however, when an individual with TBI makes a choice to stop treatment in a manner that is often referred to as *against medical advice*. In these instances, many ethical questions arise that must be addressed by the treatment team, the discharge planner, and caregivers.[7] The treatment team and caregivers may face the decision of recommending competency hearings in order to attempt to continue to provide recommended treatment. Simply put, a person's refusal to willingly follow treatment advice cannot become a reason to proceed to discharge. Banja et al. submit that clinicians have an ethical responsibility to attempt to convince people of the need for continued treatment in language they can comprehend and may also have a responsibility to recommend competency proceedings. Should competency proceedings be undertaken, it is incumbent upon the treatment team to provide clear, objective, and convincing evidence that relates to people's ability to care for themselves, obtain and maintain employment, know what to do in an emergency, and be aware of and practice safe sexual precautions. Banja et al. point out that many people with TBI can present relatively well to an adjudicator who is unfamiliar with brain injury. Thus, the treatment team must be prepared with hard facts and objective data. Of course, one also has to consider the degree to which an individual who is required to participate in rehabilitation will fully cooperate with such efforts.

Discharge disposition can be heavily influenced by the type of funding available to the injured person. Chan et al. reviewed 1,271 cases of moderate-to-severe TBI and the frequency with which individuals were placed in skilled nursing facilities (SNFs) or rehabilitation facilities.[8] Those not included in the study were people with Medicare or self-insurance coverage, people who were discharged to home or transferred to another facility, people who left against medical advice, and people who were incarcerated. It was clear that people with Medicaid coverage were more likely to have been injured by assault and had longer LOS. People with Medicaid coverage were much more likely to be discharged to an SNF than to a rehabilitation setting. People with fee-for-service insurance coverage had shorter acute LOS and were most likely to be transferred to rehabilitation settings. People with HMO coverage had a higher percentage of referral to SNFs although the difference did not reach statistical significance. The implications for recovery of function are not entirely clear for those people less likely to be transferred to a rehabilitation setting although research with a stroke population showed a clear advantage in outcome for those people who received rehabilitative treatment.[9]

Discharge disposition may also be impacted by whether a physical medicine and rehabilitation specialist has been involved in the case, either for treatment or consultation. Wrigley reviewed the discharge disposition for 756 people with TBI and found a significant difference in disposition related to the presence or absence of this specialist.[10] The study also showed direct and indirect injury severity indicators, marital status, and age impacted likelihood of referral to rehabilitation settings. The impact of age was such that older people were more likely to be referred.

A continuum of treatment has developed over the last 40 years that provides a system of treatment setting options for individuals with acquired brain injury. This continuum of treatment setting emerged in response to the complex needs observed in recovery following brain injury and recognition that recovery proceeds beyond the first few months after injury. The treatment continuum is schematically presented in Figure 35.1.

Individuals will likely require one or more of the depicted treatment settings, in particular, benefitting from involvement in multiple settings for rehabilitation. Unfortunately, nearly 64% of individuals discharged from a hospital-based inpatient rehabilitation setting actually go on to receive no more rehabilitation.[11] Discharge planning should educate the individual and family concerning the various treatment settings so as to prepare them for the notion that going home immediately may not be in the individual's best interests. Doing so may also better prepare all parties for the reality that recovery from brain injury does not occur over a short period of time. Rather, recovery can often require a protracted period of time and increased therapeutic intensity

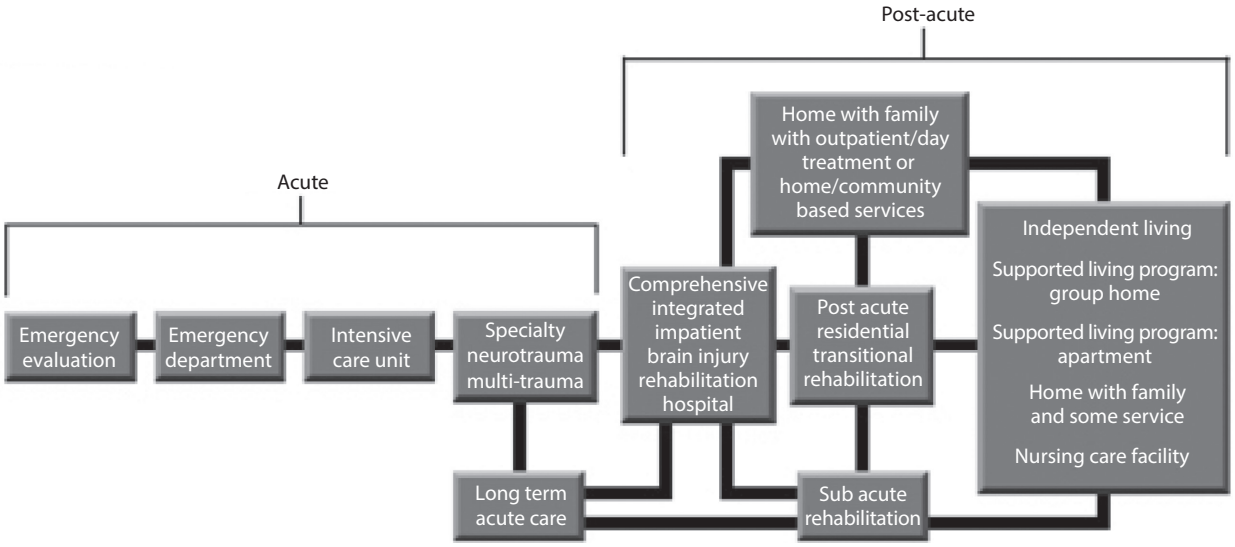


Figure 35.1 Continuum of care. (Adapted from the Rocky Mountain Regional Brain Injury Systems.)

as the individual develops medical stability and is further from the injury onset.

The purpose of this chapter is twofold: to offer a broadened view of discharge planning that extends years beyond injury and to provide insights into the nature of the long-term problems encountered with methods of addressing those problems. Much of the discussion in this chapter involves postdischarge caregivers, their needs, concerns, and education. The ethical implications of relegating the care of a person with TBI to what is, usually, a lay population without adequate financial, clinical, educational, or other resources is not a focus of this chapter. In fact, it is highly doubtful that one could reasonably conclude that sufficient resources are allocated to people with TBI and their caregivers in general. This chapter approaches the issues from the perspective of what can be done within current limitations of the managed care environment.

EARLY PROBLEM IDENTIFICATION DURING FOLLOW-UP

The sequelae of TBI can be many and varied with relatively little congruency between any two injured persons. In fact, it is only with the perspective gained by rehabilitative experience with large numbers of persons who have survived TBI that one gains a view of the wide variety of these sequelae, successful and unsuccessful approaches to them, and some commonalities that can be found in subgroups of the whole population. It is this experience that illustrates the importance of regularly scheduled follow-up contact with persons and their caregivers to identify problems before they become complicated or develop into insurmountable obstacles requiring major changes in the person's life. Such follow-up should be conducted in the days and weeks immediately following discharge and in the months and years that follow.

Job coaching, as an example, has come to be widely recognized as a successful means of accomplishing return to work.[12–14] The job coach functions to train the individual, assure that the assigned work is completed, identify barriers to success, and find requisite solutions for those identified barriers. The concept of early problem identification is equally valid when applied to the broader picture of the person's family, social, academic, and/or vocational experience postdischarge. Properly educated caregivers can sometimes be quite successful in setting up more effective discharge scenarios and maintaining them; however, they must be able and willing to participate in the early identification of problem areas and have access to resources for ideas on management of those problems. Ideally, the discharge planner has been able to provide good educational preparation of relevant potential barriers that specific caregivers might encounter for their family member as well as act as an ongoing resource for the person and caregiver. In fact, the entire rehabilitation team can often be helpful in answering questions caregivers may encounter postdischarge. The discharge planner can act as an interface to the team or facilitate more direct contact. Measures such as educational lectures, resource centers, websites, educational materials, continued consultation for ideas, and problem solving following discharge can all contribute to the ongoing education of persons and their caregivers.

As problems develop postdischarge—and they do—they often develop into greater complications than necessary, only because their significance is either not recognized early on, their cause or end point may not be recognized, or a reasonable solution to the problem cannot be identified by the people involved. Discharge planning should include the preparation of a caregiver manual (Appendix 35-A), which seeks to address known areas of concern for an injured person as well as the more likely long-term complications that may be encountered and methods for either avoiding those complications or methods to address them should they occur. Likewise, consultation should be conducted with postdischarge treaters to ensure that these

individuals are properly briefed on the specifics of the case, that adequate records have been transmitted, and that an invitation for ongoing consultation by the discharging team has been offered. This accomplishes both a continuity of care and treatment approach and provides the postdischarge treater(s) with some depth of experience that they, as individual treaters outside a comprehensive rehabilitation milieu, may be lacking.

AVOIDING REINJURY

The literature is fairly clear about the cumulative nature of injury to the brain seen with repetitive trauma.[15] Likewise, the literature is clear regarding the susceptibility of persons to reinjury following a first or second TBI.[16] As a hallmark of success of rehabilitation and in a desire to increase overall life satisfaction, normalization of routine and activities is usually viewed rather positively. Return to some aspects of life, however, may be contraindicated following TBI.

In general, the person's desired social, vocational, and recreational pursuits must be considered, balancing the level of risk for reinjury with the need to be productive and meaningfully engaged in life. There is no clear-cut, easy approach to admonition regarding such matters. For example, it may or may not be advisable to limit an individual's use of a bicycle. Although it is clear that such use should always be done with a helmet, some persons will have visual field, vestibular, or other physical deficits that make reinjury far more likely. Others may find that bicycle use is a sole method for transportation to engage in other life activities. In many cases, the best that can be accomplished is a careful review of the intended vocational and recreational activities for the potential of reinjury. Subsequent identification of high-risk activities should be made for the person, the family, and the employer with a discussion of the risks and benefits of engaging in each activity. Sexual activity, dating, job safety, and return to risky recreational pursuits, such as motocross, skiing, or snowboarding, are only some examples of issues that will arise and need to be considered over the long term. Recommendations for activity restrictions may be permanent or temporary, depending on the circumstance.

These discussions need to begin early in the rehabilitation process as they often represent major shifts in activities from which life satisfaction derives. People often have some difficulty adjusting to the idea that their lives will be affected over the long term.[17–19] It is often beneficial if they can be helped to view these changes as educated choices they are making to alter their lifestyles as a reasonable response to a major event in their lives as opposed to changes that are imposed by well-meaning health care providers and/or family members or by the injury itself. In some cases, persons with acquired brain injury have significant difficulty in understanding the nature of changes in their abilities.[20,21] They may persist with expectations that can no longer be justified based upon their actual capabilities. Early identification of such discrepancies must be undertaken in the rehabilitative process, aggressively addressed in treatment, and reflected in the discharge planning.[22]

ACTIVITIES AND ACTIVITY LEVELS

Human beings are prepared from a very early age to become productive in later life. That productivity is expressed, ever increasingly, through vocational endeavors although this is often preceded by educational preparation of one sort or another. Productivity in later life is a major source of interpersonal interaction and socialization. Those activities and facets of life that contribute to life satisfaction are largely contained within, or derived from, the pursuit of avocational and vocational interests and the subsequent social interplay that occurs.

Perhaps the harshest reality following TBI for those persons unfortunate enough to be left with significant residual deficits is the lack of access to those events and affairs in life that represent the pinnacle achievements of our adulthood and all that we are prepared to participate in lifelong. Loss of the ability to work can have demoralizing effects.[23] Social isolation and the resultant depression that often accompanies arise largely from an inability to access avocational or vocational activities meaningfully and independently following TBI.[6,24] In fact, in the United States, there is not a real societal push to provide for return to such activities. Funding for rehabilitation into these activities is not sufficient nor appropriate[25] with the possible exception of the workers' compensation system in some states. Even workers' compensation systems may frequently fail to adequately undertake vocational rehabilitation with this population. Financial disincentives exist for returning to work in the form of limited reenlistment for public financial assistance and risk of loss of income and public health insurance coverage.

The discharge planner must encourage the treatment team, injured person, caregivers, and funding source to recognize the rich therapeutic and life satisfaction benefits associated with immediate and long-term actualization of active and meaningful engagement in living. The individual must be prepared to complete as many activities of daily living (ADLs) as possible and as independently as possible before discharge. The discharge environment should encourage the injured person's participation in ADL completion and foster continued growth in areas of difficulty on a day-to-day basis. All too often, however, individuals are not left to dress themselves or feed themselves because to complete these activities to the level of independence that they may be capable of requires too much time. Caregivers may be pressed for time or patience and choose to complete the task for the injured person. Some caregivers watch the injured person struggle to complete a given series of tasks and conclude that the frustration is so great as to be emotionally painful for the person or themselves. Sometimes these caregivers can "love too much," attempting to reduce frustration by eliminating the task altogether or completing it for the person. The problem is that most people respond

to the level of environmental expectation. Caregivers who complete basic activities for the individual inadvertently strip the person of a sense of individuality and independence while unwittingly perpetuating, perhaps, an unnecessary level of dependence. The key is to educate caregivers and injured persons alike to identify reasonable levels of environmental support and expectation so as to create an environment that is hospitable yet one that fosters continued improvement.

Discharge planning should include a detailed and comprehensive resource analysis of available venues in the individual's community or region for meaningful engagement in the real world (see Appendix 35-B). Although this may be premature at a given level of treatment, engaging in this pursuit with an injured person and/or caregivers can provide them with insight into the long-term nature of the problems before them and teach them to undertake the resource analysis on an ongoing basis. The resource analysis should include options for volunteer activity, return to school, or return to work as well as information about more immediate care and treatment needs, such as pharmacy location, current and future professional contact information, durable medical equipment suppliers, and support groups. The process should review the proper timing of return to school or work to avoid premature return to either of these activities. The emotional trauma of failure in either of these environments can be considerable, and great care should be undertaken to affect a properly timed return to these activities. It can often be helpful to identify family and friends' vocational and avocational interests as potential sources of assistance early in the vocational rehabilitation process.

Likewise, the discharge planner must provide the injured person and caregivers with information as to how to best bring about a return to school or work. Unfortunately, most state-funded vocational rehabilitation programs are woefully inadequate for this population.[26] This information should include education about the laws that may govern the return and proper preparation for the return, both of the injured person and the people in the return environment. The discharge planner should prepare a list of resources that are available to help in returning to school or work. These may include specific persons within or who can consult with a school district, departments for students with special needs at a community college or university setting, or state-sponsored vocational rehabilitation service information. The chapter in this text by DePompei and Tyler provides an excellent discussion of issues relative to returning to school. Some cities have active support groups that assist persons in resource identification, return to work, adjustment to disability, day care, and assisted living.

Return to work is usually best when it is accomplished on a protracted and gradual basis. The employer of injury should be reserved as a final placement. Because vocational rehabilitation following brain injury is actually more akin to vocational therapy, return to work may require involvement in several less demanding positions that are intentionally limited in their scope and have specific purposes of reestablishing basic worker characteristics and gradually increasing the level of task complexity and responsibility to be carried by the injured worker. It is incumbent upon the discharge planner to properly prepare the injured person and caregivers with information that allows them to undertake this process with or without professional assistance. Equally important is the caregivers' preparation to recognize a return to work that is premature or poorly timed. A more detailed discussion of return to work can be found in the chapter in this text covering vocational rehabilitation.

Transportation is key to community reintegration following brain injury. Discharge planning should include information about returning to operation of a motor vehicle or alternative modes of transportation. Driving is a privilege in all states and, as such, all states have requirements for reporting loss of consciousness. Given the shortened LOS after brain injury, many visual perceptual deficits may not have been investigated, much less resolved, so driving an automobile, motorcycle, or bicycle can be extremely dangerous. Of course, cognitive and physical limitations following injury offer further reasons for caution and professional guidance in returning to driving. Reliance upon alternative modes of transportation will depend on service availability and financial resources. Buses and handicapped transportation services are available in many communities although they expose the individual to the public when the individual may not be able to properly protect oneself. Physical and cognitive impairments render many vulnerable to society's less savory elements. For those who can afford taxis or other similar services, these modes of transportation can become more reliable, especially with repeated use. Often such companies will arrange for specific drivers to assist on a regular basis and payment can be managed by payment in cash, credit card, or prearranged credit as in services such Uber or Lyft. Transportation via air, subway, boat, or train may present greater logistical challenge due to physical and cognitive impairment.

FAMILY SYSTEMS

The statistics regarding survival of family systems following return of a person with TBI to the home are disturbing. Families report increased depression, decreased ability to express feelings, decreased time and energy for social or recreational activity, and a tendency toward exercising increased control following severe TBI.[27] Lezak has suggested that the emotional disturbances and disorders of executive function in the family member with TBI contribute distinctively to family burden.[28] Education, counseling, and emotional support are recommended for families.

Lezak's observations were substantiated by a study that systematically examined family system outcome following brain injury.[29] Distressed family functioning across all domains was identified by family members. The return of a person with TBI to the home is first met with great pleasure. Lezak identified six stages of families' reactions once the stresses of having the injured family member at home

are experienced.[30] Pleasure is replaced by bewilderment and anxiety as the families' energy dwindles. Optimism diminishes, and guilt, depression, despair, and mourning follow the bewilderment. Families undergo a reorganization and, finally, an emotional disengagement.[30] Separation, divorce, behavioral problem development in children, or departure from the home by nearly adult children or siblings are all expected consequences.

Emotional responses vary somewhat by position in the family. Mothers, fathers, and siblings appear to react differently to the stresses of TBI within the family.[31–35] First, parents report increased global marital distress, reduced expression of affection, and a feeling of less spousal understanding in families in which children between 15 and 24 years of age suffer TBI.[33] Mothers report greater dissatisfaction with spousal support than fathers.[33,35] Mothers are more likely to be under a physician's care than fathers, are more likely to be using psychotropic medications, and tend to express negative emotion more than their husbands.[33] Rosenberg[34] studied spousal reaction following mild head injury. Half of the wives reported a high degree of negative impact in their relationships due to changes following TBI. Lyth-Frantz compared marital relationship impact between couples with a child with TBI and couples with a child without disabling conditions.[35] The effect of TBI was to decrease marital satisfaction; decrease satisfaction with parent–child relationships; produce greater family enmeshment; create a perception that the family's fate was a function of circumstances beyond the family's control; and decrease interest and involvement in intellectual, cultural, and physically oriented recreation. Next, siblings report that family stress is the greatest problem encountered following TBI in another sibling[32] and show significant signs of emotional distress.[31] Coping strategies used by siblings are suppression of frustrations,[32] wishful thinking, avoidance, and self-blame.[31]

The emotional trauma inflicted upon a family is tremendous and predisposes most families to disruption of the family system, sometimes with devastating consequences, such as marital separation or divorce, development of behavioral problems in noninjured siblings, and challenges to the parent–child bonds between parents and noninjured siblings. Wongvatunyu and Porter used a phenomenological method to describe changes in family systems from interviews and seven mothers of TBI survivors in summarizing those changes 6 months or more after injury.[36] The individuals with injury range from 20 to 36 years of age at the time of interview and range from 6 months to 20 years postinjury. Care requirements range from independence with ADLs to complete dependence. Communication problems range from none to unable to communicate verbally and cognitive and behavioral difficulties ranged from memory difficulties, impaired speed of processing, poor motivation, and anger problems.

Five basic themes were identified from this research: 1) getting attention from each other for different reasons now, 2) getting along with each other since the injury, 3) facing new financial hurdles, 4) going our separate ways down this new path, 5) splitting the family apart against our will. This unique line of investigation allowed tremendous insight into real-world difficulties faced by families over the long term. Some mothers reported family members simply did not understand what had happened to the injured person, and one viewed her family as being afraid and uncertain of what to say or how to act. One mother indicated her husband and family members were scared of direct involvement with her injured son, acting as though they might hurt him when they handle him. Mothers noted that some family members could not accept the changes they saw in the injured family member. Some felt more attention was paid to the individual's limitations than was warranted. Some mothers reported that other family members thought the mothers were too attentive to the injured young adults, "mothering her a little too much" (p. 321).[36]

Under the theme of "getting along with each other since the injury," there were reports that some family members were getting along like normal, some got along better than prior to injury, and some were struggling to get along since the injury.

Financial difficulties included secondary costs associated with the injury. In one instance, the individuals married and had four young children, all of whom were facing financial problems due to a lack of regular income. The grandparents, now caretakers of the adult son with brain injury, participated in the financial caregiving of the son's family. One mother quit her job to care for her son and divorced after the injury. The son's father would occasionally help out financially, but eventually his support waned. Those mothers who mentioned financial changes viewed them as fundamental and long lasting.

Two mothers moved out of the family home with the injured young adult child to another community that was close to a rehabilitation facility. The mothers believe that such separations were very difficult for the families with one mother stating, "It's changed all their lives. It's torn the family up" (p. 324).[36] Another mother stated, "It's just nothing there anymore, no family life or anything" (p. 325).[36]

Married mothers reported slightly more help than single mothers from family members. There were some reports of positive changes within the family after injury, noting that some relationships have improved or were closer than before.

Uysal et al. reviewed parenting skills of individuals with TBI and their spouses, the effects of parental TBI on children, and the effects of parental TBI on levels of depression for all family members in a review of 16 families in which one parent had a TBI.[37] One premise for this investigation is that people of child-rearing age are represented in the frequency of TBI, increasing the likelihood that children in these families will be affected by the TBI sequelae. Difficulties such as attention to detail, the ability to divide attention, memory difficulties in particular for events and conversations, time management difficulties, and organizational deficits would seemingly impact parenting. Additionally, affective

and behavioral symptoms, such as irritability, aggression, mood swings, anxiety, social withdrawal, and depression, could potentially impact family interactions. Last, inability to function vocationally would bring about not only financial challenges, but also difficulties in the modeling of a work ethic. In this study, parents with TBI reported less encouragement of cognitive competence, less achievement, and less conformity in their children compared to parents without TBI. Children's ratings showed only a difference in the parent behavior ratings along the dimensions of "lacks control." Overall, the differences appeared to involve less goal setting, less encouragement of skill development, less emphasis on obedience to rules and orderliness, less promotional work values, less nurturing, and lower levels of active involvement with children. Parents with TBI and their children had a greater tendency toward depression.

Members of a family can generally be expected to survive the immediate and long-term consequences experienced when a family member is injured. However, the quality of that survival should be actively discussed and planned. Families function in complicated patterns of individual and group behaviors and settle into a manner of living that becomes more or less the norm for that group. As catastrophic injury and disability enter the picture, the customary rhythm of a family is severely disrupted.[27,28] Family resources of time, attention, financial resources, and energy tend to become focused on the injured family member, sometimes to the near exclusion of all other needs. This phenomenon has been partially described as a *command performance* wherein a family member meets unbelievable physical and emotional demands on a protracted daily basis, seemingly without regard for his or her own needs, health, and welfare. Although such a "crisis" mode of operation can be useful for short periods of time, a diagnosis of TBI usually heralds the family embarkation upon a prolonged change in their way of living.

In the early stages of rehabilitation, families are sometimes reluctant to believe outcome prognostications that may be provided, viewing them as inaccurate and pessimistic. Many families report having been told that their family member may die, and if he or she does not die, that he or she may be severely disabled. These comments are often interpreted as being told their family member was going to die or that he or she would be severely disabled for the rest of his or her life. The result is a loss of credibility suffered by treaters down the line through no one's fault but circumstance alone. Such misperceptions may be avoided by active pursuit of a planned educational format by the treatment team that covers a number of topics regarding the nature of injuries sustained, their treatment, and both near- and long-term issues for caregivers.

In these early stages of rehabilitation, families respond best to access to information about their specific family member's condition and possible future care requirements. McMordie et al.[38] found a high sense of hopelessness communicated by professionals to families and injured people as reported in postdischarge surveys. Provision of a range of possible outcomes is easier to accept for many families and probably most accurate. This approach engenders a desire for more information about which outcome might be best achieved and how. McMordie et al. also found the greatest consumer dissatisfaction with information provision, specifically information about available resources, long-term outcome, and personality change following TBI. Resource centers that provide families and injured persons with detailed information that is easy to understand and readily available can be most helpful. McPherson et al.[39] support these assertions in their finding that families interviewed just 6 weeks after discharge from acute rehabilitation indicated their primary need was more information although these needs were not spontaneously presented. Instead, their need for information required prompting to be made known.

Likewise, counseling from either experienced staff or family members of other individuals with TBI who can provide good peer support can be helpful in preparing families for the challenges that lie ahead. An analogy to racing can be useful, comparing the coming weeks, months, and years to a marathon rather than a sprint of a few days or weeks. Of course, treaters are often reluctant to engage in such discussions for fear of unnecessarily removing the element of hope from the picture for patients and/or their families. Great sensitivity is required in the pursuit of information provision, education, and preparation while continuing to encourage realistic levels of hope.

Families are rarely ready to hear the need to care for themselves, feeling as though such a response would be unwise, risky, selfish, or all of these. They are, likewise, not prepared to hear that their family member is either perilously close to death as in the early stages of moderate-to-severe injuries and that, should he or she survive, they should begin to plan for such huge changes in their lives. Given the very short time frames associated with acute hospitalization, the discharge planner may be reluctant to contribute to the stresses of an already overwhelmed family. This dilemma contributes to the lack of preparedness most families report.

Families must be encouraged to both plan and actively return to normalized patterns of family living. The initial disruption of such patterns can develop into a new norm for families if allowed to continue unchallenged. Families may need assistance in learning to discuss their concerns and fears. Although this may be expected of younger family members, facilitated discussions with adult family members and friends can be exceedingly helpful for those participating directly and in modeling how to conduct such discussions with children, siblings, extended family, and friends in the future. In fact, families should be directed to talk openly about their concerns and fears, especially facilitating these discussions between couples, parents and children, and family members and friends. This should include factual information about injuries sustained, treatments provided, future treatment needs, and preparation for future stages in recovery and return home. Families need to be

educated about the various treatment facilities that may be available locally, regionally, and nationally. They should be made aware of the various levels of care frequently encountered, including acute care, acute rehabilitation, subacute care, residential and outpatient postacute services, home and community treatment, and assisted living services. They should be provided with all the treatment options and explanation as to which will be available to them based upon financial constraints individual to their situation. Although some of these services may not be appropriate or even available, the discussion will help the family to understand, from a slightly different perspective, the challenges they will be facing. This information can be provided in the form of informational pamphlets, counseling sessions, or other educational formats.

Families may need assistance in identification of assumptions within the family that may bias services that an injured person receives. Topics such as cost, geography, expertise of treaters, and objective comparison of various treatment options can be helpful. Treaters must recognize the need to investigate treatment options available locally, regionally, and nationally and balance this with the somewhat parochial tendencies professionals gravitate toward with reference to beliefs regarding their own competencies and those available at other treatment settings. Many professionals believe they are able to provide for their patient's needs adequately, but this belief may inadvertently portend a blinding to other more specialized or expert services available. This is particularly poignant for treaters at the acute and postacute rehabilitative treatment level. As LOS has decreased for acute hospitalization and acute rehabilitation services,[3,4] professionals must familiarize themselves with the multitude of postacute treatment options available today and actively advocate for their patient's access to these highly specialized models of treatment. High employment turnover in health care, however, serves to frustrate the acquisition of in-depth understanding of treatment resource availability and how to facilitate access.

Parents of injured children naturally rally around the injured child, all too often subjugating the needs of siblings and themselves. This approach may be acceptable on a very short-term basis; however, it should not be encouraged on a protracted basis. An aunt, uncle, family friend, or grandparent usually cannot supplant a parent for children. Parents should be encouraged and assisted in frank, age-appropriate discussions with siblings about the injury and the future. Of course, care must be taken to consider the emotional health and readiness of each child on a case-by-case basis, but generally speaking, children deal best with factual information. Additionally, the family will be challenged as never before to deal with high levels and ranges of emotion and may be unprepared to recognize key differences in coping strategies exercised by different people in the family circle. Failure of family members to recognize and deal appropriately with such differences in coping strategies can lead to tremendous misunderstandings and misgivings. As has been evidenced in numerous families, such misperceptions have actually contributed to deterioration and, sometimes, dissolution of family structures.

Gan et al. undertook research to identify predictors of family system functioning after acquired brain injury.[29] Greater distress in family functioning was noted by individuals with acquired brain injury, mothers, spouses, and siblings. Fathers and offspring did not report greater distress in family functioning. Problem solving was observed to be an area of difficulty along with rule changes in the family.

An overall increase in responsibilities for caregivers has been previously reported along with challenges of adjusting work responsibilities in order to manage time and availability for care for the injured individual.[32,40] Hall et al. found gender to be associated with family functioning, in particular for families of females with acquired brain injury.[40] The authors speculate that impulsivity, a lack of inhibition, egocentricity, and a change in the nurturing nature of the individual might constitute "out of role" behavioral change. Finally, the study indicated the importance of utilizing a family systems approach in dealing with the immediate and longitudinal consequences of brain injury within families.

Families need information on the importance of establishing and using a structured routine once the injured person returns home. Ironically, structure leads to freedom. The injured person needs as much external assistance as possible in organizing the environment and events. Predictable routines aid in organization of the return home for all parties and enhance the redevelopment of self-care skills in particular. Some families function well with such direction because they functioned in a structured fashion prior to injury. Other families, however, may not have functioned in such a way and may need a fair amount of help in learning to do so. Families need to understand the importance of a regular schedule for waking/sleeping, medications, meals, hydration, exercise, and completion of ADLs. An approach that is haphazard not only causes confusion but also brings risk associated with missed medications, meals, fluids, or rest. Likewise, because rehabilitation is benefitted by maximized repetition, complete participation in ADLs to the fullest extent possible by the injured person will bring about the fastest return of these skills.

Last, caregivers should be advised regarding the provision of feedback and consequences for inappropriate behaviors they may encounter. Sometimes, families are at a loss as to whether feedback should be provided for asocial behaviors. Although feedback can be overdone, generally, it is best for the family to be taught to deliver appropriate feedback and consequences for asocial behaviors. They should be taught how to deliver consequences immediately after the behaviors occur. If a behavior analyst or psychologist is available, such programming should begin in the treatment setting with instruction given to caregivers on continuation of the programming following discharge. A more detailed discussion of behavioral interventions can be found elsewhere in this text.

CAREGIVER CONCERNS

Responsibility for caring for the individual, long after formal rehabilitation has ended, usually falls to the family. The role of caregiving is demanding and typically lasts for the lifetime of the individual. Families are often ill prepared to take on caregiving responsibilities.[41] Issues reported by family members include family strain, depression, burden, anxiety, psychological distress, social isolation, loss of income, and role strain.[40,42–50]

Reduced and restricted LOS have resulted in placement of persons with TBI in the home setting far earlier than is, perhaps, best for the individual in some cases. The burden placed upon caregivers cannot be overstated. Caregivers are faced with myriad potential medical complications that may not have been adequately identified during hospitalization or may not have been manifest during that time. Most homes are not built with the anticipation of dealing with the needs of a person with physical handicaps, and, in a similar vein, most families are not equipped to deal with the pervasive demands created by a person with medical, physical, cognitive, communicative, and/or behavioral problems. Premature home placement relegates the individual to the rigors and vagaries of medicine practiced on an outpatient basis. In order to properly engage in outpatient medicine, the individual ideally is able to reliably and accurately report on his or her condition, changes in the condition, effectiveness of prescribed treatment, careful follow-through with treatment directions, and recognition of treatment failure as well as manage scheduling and coordinating multidisciplinary medical and rehabilitation appointments, arranging transportation to appointments, general oversight of the entirety of the individual's likely complex clinical presentation, management of family system constraints, and financial management for medical treatment costs at least. Any one of these and usually many more than one of these can be expected to be seriously impacted by the brain injury itself, meaning that an outpatient approach applied too early is destined to be far less effective than one might expect from outpatient medical management in general.

Many of the concerns noted are shared by the injured person and caregivers alike, including fatigue, mood disturbance, and overall life dissatisfaction.[49] These complaints are reported by many levels of involvement by caregivers, extending well beyond the primary caregiver to secondary and tertiary caregivers. The primary caregiver is most often a woman, usually a wife or mother.[1,49] In a population studied in which the mean age of the person with TBI was 28 years, 64% of caregivers were the parent of the injured person, and 25% were the spouse.[51] The mean age of the caregiver was 44 years, suggesting a fairly long future of management of such responsibilities. Seventy percent of the caregivers lived in the same residence as the injured person.

Measures of life satisfaction demonstrate a progression as chronicity increases. In the first year after injury, employment was associated with life satisfaction, and age, marital status, social integration, and depressed mood were not. However, in year 2 postinjury, employment, social integration, and depressed mood were associated with life satisfaction.[6] This progression may be due to recognition of the permanence of sequelae of the brain injury as time progresses. Given the findings on the relationship between quality of life and employment, it appears that persons with TBI who are able to become gainfully employed or productive on a day-to-day basis experience greater life satisfaction.[6,24]

Kreutzer et al. reviewed employment stability patterns during the first 4 years after TBI and found that minority participants were more than twice as likely to experience unstable employment patterns.[52] A contribution to postinjury differences in outcome has been suggested to be related to preinjury differences between racial groups in the United States, which include lower educational levels, lower income, less employment stability, and poor insurance coverage for minority populations. Minority group members are more likely to have violence as an etiology of injury.[53,54] One study indicated that more than one third of African American subjects have violence as an etiology for injury compared to less than 3% of White subjects.[55] Examination of racial differences in caregiving patterns, caregiver emotional function, and sources of emotional support following TBI showed that proportionately fewer African American caregivers were spouses compared to White caregivers. Caregivers as "other relatives or friends" were two times more prevalent in African American caregiving. The largest nonspouse, nonparent caregiver group was siblings in the African American study sample followed by other relatives, grown children, and boy- or girlfriends. Less than 5% of caregivers fell into any of these categories for White caregivers. The majority of caregivers lived with patients in both groups. The study demonstrated adverse effects of emotional distress and satisfaction with life as level of disability increased, and there were no differences between racial groups along these parameters. More Whites than African Americans received psychological treatment or counseling.[56,57] Caregivers should be prepared for their responsibilities to both endure over a long period of time as well as their burden of care to increase over time, especially so as severity of injury increases.[58,59] Brooks et al.[58] found that the 10 most frequently encountered problems reported by relatives remained either stable or increased in the majority from 1 year postinjury to 5 years postinjury (Table 35.1). In fact, the largest increase in frequency of reporting was in the area of disturbed behavior at 5 years. Threats or gestures of violence increased from 15% at year 1 to 54% at year 5. Twenty percent of relatives reported their family member to have been physically violent, involving actual assault at year 5, an increase from 10% at 1 year postinjury.

Caregivers may need to take on the role of nurse, therapist, educator, counselor, vocational rehabilitation counselor, social worker, case manager, and life care planner in addition to their other responsibilities. Holland and Shigaki[60] point out that education of a caregiver early in the acute treatment phase may be limited in its efficiency due to the

Table 35.1 Ten problems most frequently reported by relatives at 5 years (n = 42)

	Percentage relatives reporting	
Problem	1 year	5 years
Personality change	60	74
Slowness	65	67
Poor memory	67	67
Irritability	67	64
Bad temper	64	64
Tiredness	69	62
Depression	51	57
Rapid mood change	57	57
Tension and anxiety	57	57
Threats of violence	15	54

disruption of the continuum of recovery that can be encountered due to a lack of rehabilitation programming continuity from acute rehabilitation through community reentry. These authors suggest a three-phase approach to provision of educational materials to caregivers, depending upon the phase of recovery of their family member. The authors suggest that a resource listing of published educational material and local care resources be provided, over time, to caregivers, and the authors provide a listing of such bibliographic resources for the reader.[60] DePompei and Williams outline a family-centered counseling approach that is useful during rehabilitation.[61] Acorn developed a guide for community-based family education and support groups to provide education regarding TBI and its sequelae, enable families to identify community resources, and build support networks among families with TBI.[62] Of particular relevance to loss associated with trauma, the work of Pauline Boss provides useful, practical, and well-conceptualized consideration of the psychological consequences of loss without finality.[63,64] In brain trauma, the loss of previously defined self or of the previously defined personality of a family member constitutes an ambiguous sort of loss that continues for all except those who cannot recall self. To that end, counseling with a professional versed in these concepts may be a useful discharge resource.

Spirituality and faith can be seriously challenged by the tremendous trauma that sudden injury can bring. Although some find real and important solace and comfort in their faith, others may find their beliefs shaken, sometimes with great anger toward their faith, church, or God. All too often, these issues are not explored in the context of rehabilitation. Although a spiritual life may not be for everyone, it is important to many patients and/or their families.[65] Reengaging them with their faith can be of great importance in furthering their reentry into their community and in providing comfort and familiarity in their journey. As discharge planning considers long-term satisfaction with life and the individual and family's subjective level of distress, ensuring a connection to spirituality and/or religion has been associated with better outcomes in each of these dimensions.[66]

SEIZURE HYGIENE

The overall incidence of posttraumatic epilepsy (PTE) is estimated at about 5% for all persons with nonmissile head injury.[67] The incidence of PTE following moderate head injury is 1.6% and, following severe head injury, is 11.6%.[68] The overall incidence for PTE has been noted to be as high as 25% and up to 35% for persons comatose for 3 or more weeks.[69] In the 1980s, seizure prophylaxis was somewhat common in the United States, and in Europe, the more prevalent approach was that of the "free first fit." Anticonvulsant coverage was provided in the United States to attempt to prevent the first seizure, and in Europe, such coverage was provided after evidence of a first seizure. A study by Temkin et al. demonstrated no real long-term benefit associated with prophylaxis coverage, and as a result, this practice in the United States has slowly decreased.[70] In fact, a more considered approach to prophylaxis is generally followed, taking into account the nature of the injury and the likelihood of PTE associated with that type of injury.

PTE can first occur many years postinjury.[71,72] It is important to advise persons with TBI and their families about their relative risk for the development of seizures and factors that are within their control that may impact the nature of a given seizure disorder. Families should be educated as to what constitutes seizure activity. Grand mal seizures are easily recognized, and partial motor seizures may be less recognizable. Clearly, complex partial seizures are least recognizable although they constitute a surprisingly high percentage of seizure prevalence following acquired brain injury.[73] Complex partial seizure disorders are difficult to diagnose and may be misinterpreted as psychiatric conditions by caregivers and professionals alike.

Medication compliance represents a primary area of concern. The person must understand the medication regimen that has been prescribed. This includes the importance of compliance with the timing of medication administration and understanding whether and when a missed dosage can be made up. For example, missed dosages of some anticonvulsants, although best taken at prescribed times, can be taken at any time in the same 24-hour period that the missing dosage is prescribed. Other anticonvulsants, however, cannot be handled in a like manner. Education must be provided as to the specific characteristics and options of a given anticonvulsant coverage.

Likewise, it is important for persons and their families to understand whether an anticonvulsant can be abruptly stopped. The cessation of medication may be due to a prescription lapse; unavailability of the medication due to travel; forgetfulness; financial concerns; incarceration; or a directive from an uninformed health care provider, family member, friend, or the injured person to simply stop the medication. Some anticonvulsants and antispasmodics require a tapering so that seizures are not actually precipitated.

It is also wise to educate regarding sleep, rest, and stress. Many persons with seizure disorders experience increases in the frequency of seizure activity with increased fatigue and stress. Education regarding monitoring of drug levels during periods of diarrhea or constipation can be important for the person with a relatively fragile seizure disorder as drug absorption can be impacted by such conditions.

Information regarding maintenance of adequate hydration should be provided. People who live in arid climates; who may travel extended distances by airplane; or engage in outdoor activities, such as hiking, backpacking, or river trips, should be advised to carefully monitor noncaffeinated and nonalcoholic fluid intake, both by noting the quantity per day and the frequency and nature of urination. Education regarding the diuretic effect of alcohol and caffeine should be provided.

Last, some anticonvulsants may interact with other drugs, either increasing or decreasing the other drug's effectiveness or increasing or decreasing the serum levels of the anticonvulsant coverage.[74] Specific information about these drug interactions must be provided to the person and his or her family so that they may monitor future prescription use for potential interactions. Although this is a role that is best filled by the health care provider and/or a pharmacy, these individuals may be unable to fill this role due to lack of information or lack of access to the person's complete medical history.

DEPRESSION

Depression is identified as a significant long-term complication by numerous authors.[75–78] Studies that look out 3 to 7 years postinjury point to depression as a major complaint by both injured persons and their caregivers.[76–78] The advent of the SSRI class of antidepressants has been an important development in the treatment of persons with TBI.[79] This particular class of drugs appears to be tolerated well, in general, and has a low complication rate.

The etiology of depression appears to be twofold: biochemical and situational. Social isolation is considerable and arises from diminished real-world interaction. This diminution can be traced, in part, to a lack of avocational or vocational involvement together with frequently impaired interpersonal skills.[80,81] Both contribute to substantial social isolation. Most persons with TBI are quite able to recognize the differences in their lives, comparing pre- and postinjury status. In the absence of meaningful involvement in the regular workaday world, feelings of isolation, frustration, and depression are commonly reported. Discharge planners should educate injured persons and their caregivers to participate in fitness and aerobic exercise routines that have been medically approved to assist with fatigue and depression. It is wise to educate regarding the symptoms of depression. This should include agitated depression, panic attacks, and anxiety.

The discharge planner can address this issue by education and encouragement to establish meaningful involvement for the person's capability postdischarge. Likewise, the discharge planner can make the injured person and the caregivers aware of counseling services and church or community support groups that may operate recreational, avocational, or vocational activities as well as the value of counseling and antidepressant medications in consultation with their physician. There must be a careful tie-in to development and maintenance of appropriate activity levels and meaningful involvement in both the home and community.

Many people with TBI report frustration at the loss of choices and control in their lives postinjury. Aware caregivers can provide an increasing array of choice and control in daily decision making, gradually turning more and more control over to the injured person as he or she is able to accept it. Because this is an ongoing and continually changing process, caregivers must understand the need to be vigilant and reexamine choice/control issues on a regular basis. Families sometimes attempt to exert maximal control after a family member is catastrophically injured,[27] perhaps in an attempt to limit their exposure to future disastrous events. Some gain control over other aspects of life previously managed by the injured person (e.g., finances) and are reluctant to give up or share that control. Still others sense a need to exert control to prevent a person with impaired judgment from becoming financially, legally, emotionally, sexually, or socially encumbered beyond his or her capability. The need to protect stands in opposition, in some cases, to the pursuit of life satisfaction and participation in age-appropriate activities. The interaction of risk with freedom of choice and balancing rights to self-determination, life satisfaction, and safety should be actively discussed on an ongoing basis.

These matters can become quite complicated, and professional counseling best assists most families. Discharge planners are well advised to make contact with mental health professionals in an injured person's home area that are experienced with TBI and can offer occasional assistance and counseling on an as-needed basis.

SLEEP

Sleep disturbance is a relatively common complication following TBI. Sleep disturbance can be manifest in three primary problems (although a multitude of problems can be encountered): 1) sleep apnea/hypopnea, 2) periodic limb movement disorder (PLMD), and 3) hypersomnolence (excessive daytime sleepiness). Interruption of sleep is a fairly common complaint following TBI and may be related to routine, diet, psychological issues, or sleep hygiene. Education should be provided regarding each of these impacts to the injured person and his or her caregivers as they may be most easily addressed. More complicated issues, such as sleep apnea/hypopnea, PLMD, and hypersomnolence, will require medical interventions. It is beyond the scope of this chapter to thoroughly review sleep disorders. Rather, the intent is to review some of the more common issues that may be encountered following TBI.

In the general population, the prevalence of sleep apnea/hypopnea is estimated to be between 2% and 4%.[82] PLMD is estimated to occur in 5% of the population,[59,83] and hypersomnolence occurs in 0.3% to 13% of the general population, depending upon definitions used.[84,85] By contrast, sleep apnea/hypopnea has been evidenced in 11.3% of persons with TBI, PLMD in 25.4%, and hypersomnia in 29.6%[86] in a study of 71 consecutively enrolled persons admitted to a postacute residential rehabilitation program. An interesting finding in this study was that persons with hypersomnolence were often unable to perceive their hypersomnolence, and the researchers suggested routine sleep laboratory evaluation. Castriotta and Lai studied 10 persons with TBI who reported hypersomnolence. These individuals averaged 110 months postinjury.[87] Treatable sleep disturbances consisting of obstructive sleep apnea, upper airway resistance syndrome, central sleep apnea, and/or narcolepsy were found in all 10 cases. Three individuals had a preinjury history of hypersomnia, and of these three, two actually sustained TBI from motor vehicle collisions while driving with the suspicion that they may have fallen asleep at the wheel.

Finally, in a study of 184 persons who complained of excessive daytime sleepiness after head or neck injury, multiple sleep latency testing showed mean sleep onset time of less than 5 minutes in 28% of the subjects and less than 10 minutes in 82%.[88] Awareness of hypersomnolence did not correlate with the objective findings. Sleep-disordered breathing occurred in 32% of the persons studied.

Sleep has been associated with cognitive function, behavioral functioning, and psychological health.[86,89–91] Likewise, sleep apnea has been associated with motor vehicle collisions[92,93] and unintentional injuries.[94] These data reflect potential contributory factors to an initial TBI as well as to likelihood of reinjury, either due to trauma or chronic hypoxemic events.

The discharge planner should provide education regarding signs and symptoms associated with sleep disturbances and possible links to reinjury as well as information regarding diagnosis and treatment in cases in which these issues have not been thoroughly investigated prior to discharge.

LONG-TERM PSYCHOLOGICAL ISSUES

There are numerous issues with regard to psychological well-being that persist beyond the initial brain injury. Bergland and Thomas used a case study approach to describe changes in functioning for 425 adolescents who sustained TBI.[95] Seventy-five percent of the individuals' parents reported a change in the persona of the individual recognized by that individual. Parents decided exaggerated emotions and behavioral excess or deficit contributed most to the impression of the different personality. Worry, anxiety, fear, frustration, anger, and withdrawal were frequent emotional reactions of individuals when confronted with the reality of their injury in everyday environments. A loss of ability and self-esteem were reported with these changes in awareness. Parents reported increased time and effort for all activities were required and that this added to the strain and difficulty of managing life postinjury. The impact on social relationships was such, that although friends were supportive of the individual during hospitalization, relationships tapered off once the permanence of deficits became apparent. This was hurtful and disappointing to most of the adolescents, and the parental response was one of intense pain at sight of their child's suffering with parental attempts to buffer the loss and hurt for their child. Most reported difficulty in establishing and maintaining new friendships as well as confusion and hurt over lost friendships.

Parents discussed the disappointment, loss, and grief associated with the perceived loss of their child's future. Conflicts that affected family roles and marriage and sibling relationships were reported. For those who returned to school, many reported an unrealistic workload at school and a lack of understanding and insufficient assistance within the school setting and with managing classroom responsibilities and workload. A few quit school because of academic or injury-related difficulties. Most returning students and families reported the return to school experience to be difficult, disappointing, and frustrating.

Hibbard et al. utilized the Structured Clinical Interview for DSM-IV Personality Disorders to survey for 12 Axis II personality disorders in 100 individuals with TBI between the ages of 18 and 65.[96] The individuals averaged 40 years of age and 7.6 years postinjury. The highest prevalence of Axis II disorders was found for antisocial personality disorder, obsessive–compulsive personality disorder (OCD), paranoid personality disorder, and narcissistic personality disorder. Personality changes endorsed by more than 30% of the sample postinjury reflected loss of self-confidence, attempts to cope with cognitive and interpersonal failures, and negative affect problems. The authors felt the findings argued against a specific TBI personality syndrome and supported instead the diversity of personality disorders reflective of the persistent challenges and compensatory coping strategies developed.

Hibbard et al. report the incidence of mood, anxiety, and substance use disorders in individuals with TBI following review of 100 adults between the ages of 18 and 65 years who averaged 8 years postinjury at the time of the study.[97] Data was collected by interview, and the authors attempted to identify diagnoses of major depression: dysthymia, bipolar disorder, anxiety, diagnoses of panic disorder and phobia, and substance use disorders. A significant percentage of individuals presented with substance use disorders prior to TBI. The most frequent Axis I diagnoses were major depression and specific anxiety disorders: posttraumatic stress disorder (PTSD), OCD, and panic disorder. They found 44% of individuals presented with two or more Axis I diagnoses postinjury. Individuals with a history of pre-TBI Axis I disorders were more likely to develop post-TBI major depression and substance use disorders. Rates of disorder resolution were similar for individuals regardless of preinjury psychiatric histories. Anxiety disorders were least likely to remit.

Draper et al. investigated the relationship between demographic variables, injury severity, cognitive functioning, emotional state, aggression, alcohol use, and fatigue at 10 years postinjury following TBI in 53 individuals ranging in severity of injury from mild to very severe.[98] Generally speaking, the incidence of clinically significant anxiety increased in a stepwise fashion with severity of injury with the exception of distinguishing between severe and very severe injuries with which clinically significant anxiety was 33% and 22%, respectively. Interestingly, the presence of clinically significant depression decreased as severity of injury increased, ranging from 67% in mild injuries to 35% in very severe injuries. Individuals with more severe anxiety and depression had poorer psychosocial functioning. Fatigue and aggression were also found to be important issues at 10 years postinjury. Aggression was a significant problem for 12% of individuals studied, and fatigue was found to be a strong contributing variable. High levels of alcohol use were also associated with more severe aggression with 32% of participants using alcohol at "potentially harmful levels."

Hawley and Joseph surveyed 165 individuals with TBI to investigate long-term positive psychological growth. Follow-up was conducted a mean of 11.5 years postinjury.[99] Evidence showed that individuals are capable of positive growth following brain injury. There was no difference noted between those with mild versus severe injury. The degree to which an individual experienced positive growth was negatively correlated with anxiety and depression present at follow-up, suggesting a positive outlook was associated with low anxiety and depression. Higher levels of growth appeared to be associated with better psychological adjustment.

Hoofien et al. reviewed psychiatric symptomatology, cognitive abilities, and psychosocial functioning in 76 individuals with severe TBI, averaging 14.1 years postinjury, comparing findings of individuals with injury to those of their families.[100]

Figure 35.2 illustrates elevations in psychiatric symptomatology related to hostility, depression, anxiety, psychoticism, OCD, somatization, and phobic ideation reflecting overall psychiatric distress for individuals with injury. Figure 35.3 illustrates psychiatric distress reflected by families of individuals with brain injury. Family members showed elevations in anxiety, hostility, somatization, depression, and phobic ideation. Correlations were observed between psychiatric symptoms and behavior patterns. High levels of distress correlated with greater exhibition of behavioral disturbance and difficulty in acceptance of disability. Significant negative correlations were observed between level of functioning and acceptance of disability, indicating that the lower the acceptance of disability, the higher the psychological symptomatology. Persistent deficits in intelligence, memory, learning, manual speed, and dexterity were noted.

Of 76 individuals with severe TBI (mainly, coma equaling 14 days) in the study, 28 were reported as competitively employed. Eighteen were considered engaged in noncompetitive employment settings. Only 10 individuals reported salary as their main source of income with 45 individuals reporting their main source of income to be compensatory allowances, three relying mainly on family support and 18 identifying various combinations of the above as their main source of income.

With reference to family functioning, significantly fewer individuals were married, and the prevalence of divorce was

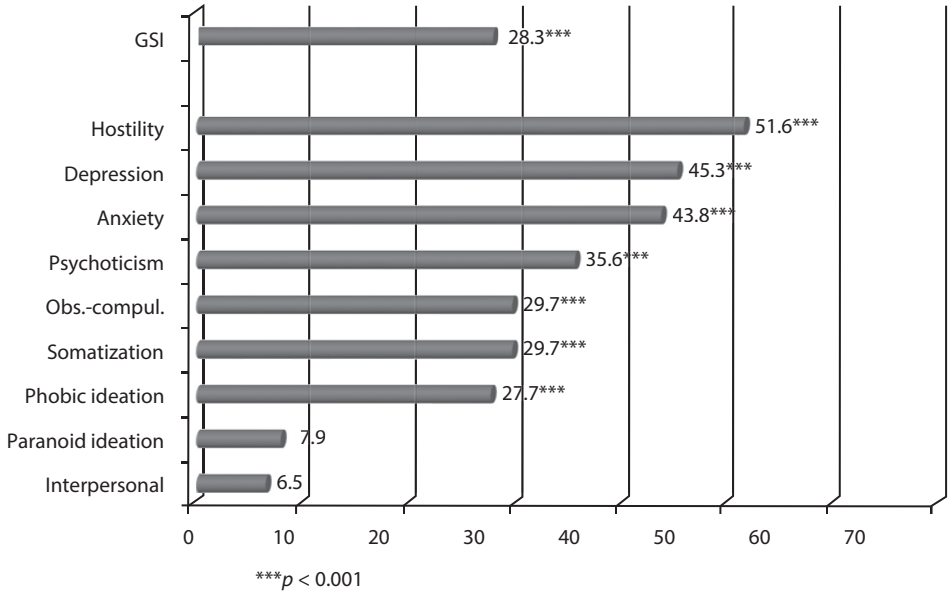
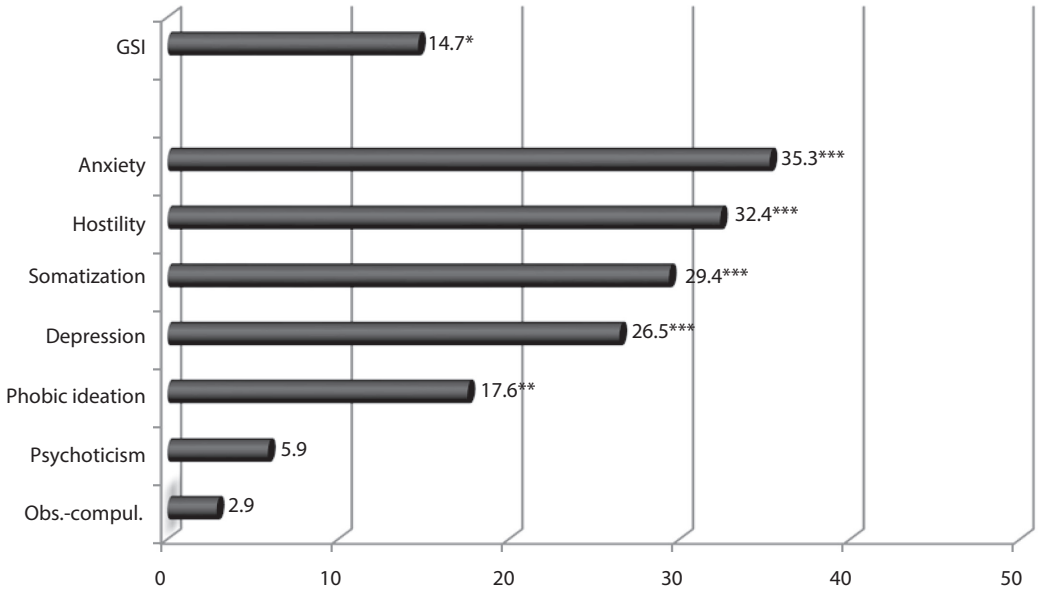


Figure 35.2 Percentage of patients with significantly elevated SCL-90-R and GSI scores.



*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$
Note: Paranoid ideation and interpersonal sensitivity were endorsed below the 95th percentile.

Figure 35.3 Percentage of family members with significantly elevated SCL-90-R and GSI scores.

higher when compared to the cultural norm. Social functioning was evaluated by reports of numbers of friends and type of social engagement. Participants reported an average of 2.7 friends, and 19 individuals reported they had no friends at all outside the family. Five indicated they had no social support at all.

In a small preliminary study, McGrath and Linley found some evidence for progression in what they referred to as posttraumatic growth following acquired brain injury.[101] In comparing matched samples in which one group averaged 7 months postinjury and the other group averaged 10 years postinjury, it was possible to discern some progression in posttraumatic growth over time. Items that were most strongly endorsed for both groups included the following: 1) appreciation of life, 2) relating to others, 3) personal strength, 4) new possibilities, and 5) spiritual change. The 10-year postinjury group had higher endorsement of change in understanding of spiritual matters whereas this area was not endorsed in the 7-month postinjury group. These authors suggested that positive change may take many months to develop and that "a degree of unpleasant engagement with the reality of the long-term situation may be necessary" (p. 772).

Finally, Powell et al. investigated the time course and characterized positive psychological changes after TBI comparing two groups of individuals with brain injury in a long-term follow-up study.[102] The first group was comprised of 23 individuals who averaged 1.7 years postinjury, and the second group was comprised of 25 individuals who averaged 11.6 years postinjury. The authors looked for correlation between posttraumatic growth and other factors, such as life satisfaction, anxiety, depression, and severity of injury. They investigated each individual's subjective perception of his or her experience, the significance of the event for him or her, positive and negative lifestyle and personal changes that had been made, perceptions of good and bad advice for coping, and the factors that aided with adjustment. Not surprisingly, life satisfaction was found to be negatively correlated with anxiety and depression and positively correlated with the degree to which individuals endorsed perceptions that their life had been ruined.

Figure 35.4 illustrates factors that have been identified as helpful in adjustment to life after injury and suggests that social support from family and friends and personal

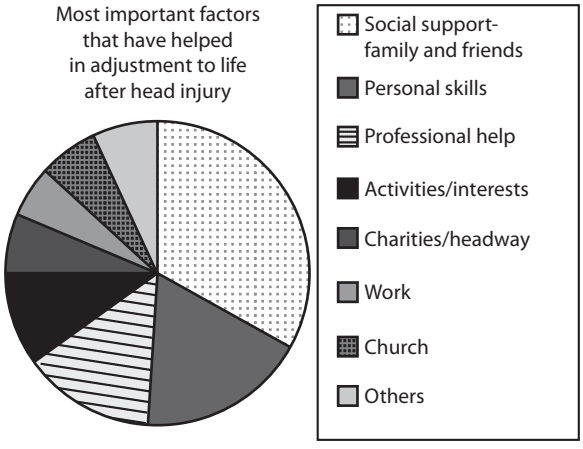


Figure 35.4 Whole samples response to question: "What are the most important factors that have helped in adjustment to life after head injury?"

skills were most helpful. Figure 35.5 illustrates perceived positive changes in self and lifestyle with two most frequently endorsed findings being that the individual appreciated people in life more and had positive changes in lifestyle. Figure 35.6 illustrates advice that was found to be helpful with the two most frequently reported being "it takes time; you will improve; time is a healer" and "don't give up; have a positive attitude." Advice that was considered to be the worst is illustrated in Figure 35.7 with two most frequently reported as "act as if nothing happened" and pessimistic comments offering no hope.

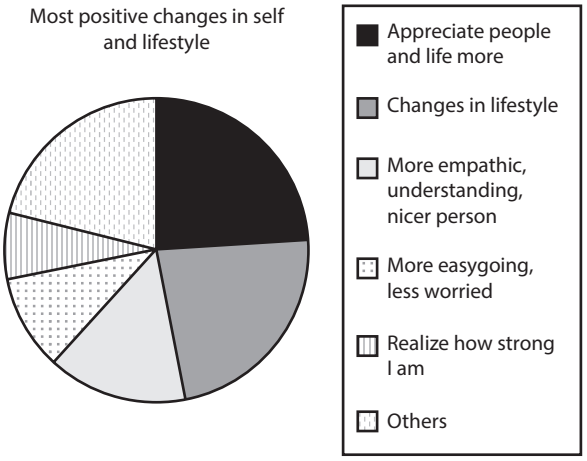


Figure 35.5 Whole samples response to question: "What are the most positive changes in yourself and your lifestyle following your head injury?"

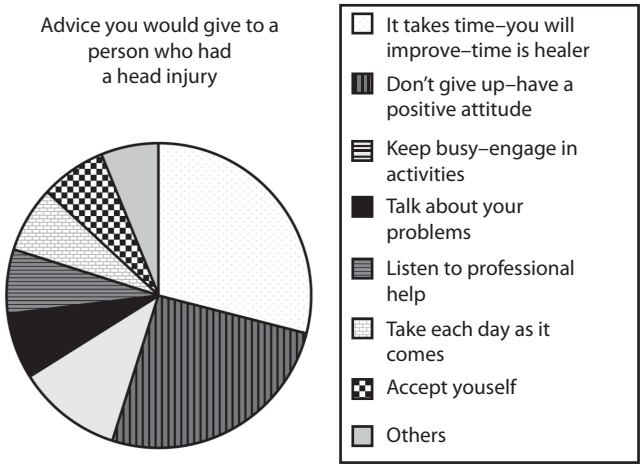


Figure 35.6 Whole samples response to question: "What is the best advice you would give to a person that has just had a head injury?"

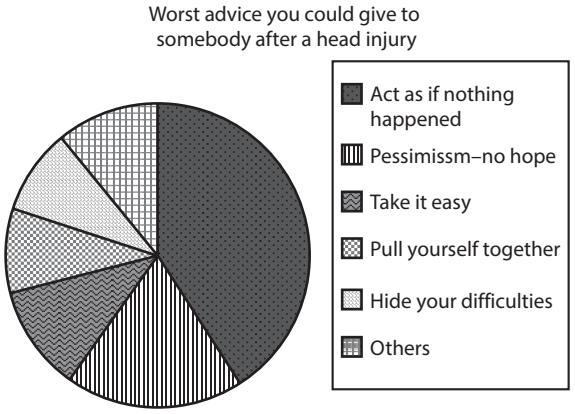


Figure 35.7 Whole samples response to question: "What is the worst advice you could give somebody after a head injury?"

CRISIS MANAGEMENT

Few families can be expected to be prepared to manage the various types of crises that arise for persons with TBI and their caregivers. Davis et al. conducted research using a triangulated research strategy involving both qualitative and quantitative methods to better understand the experience of crisis following brain injury.[103] Triangulation involved information derived from individuals with brain injury, their families, and professionals involved in their care in community-based settings.

Although crisis is usually thought of as a temporary state of upset and disorganization, the results of these authors' work suggest that the experience of crisis after brain injury is somewhat different. Whereas crisis is usually thought of as time-limited, crisis following brain injury was more regularly characterized as "never-ending." Participants described crisis as a lifelong condition in which coping was dependent upon an individual's ability to redefine one's identity. There was indication that crisis varied in intensity from time to time, but it was never really absent. The authors described crisis as receding somewhat, leaving the individual and family with a "precarious homeostasis" during periods of crisis recession.

Simply put, crises emerge when the nature and number of demands exceeds the existing capacities of an individual or a system.[104] After brain injury, both the nature and number of demands change drastically. Individuals and families are placed in a confusing series of circumstances, the likes of which they have most likely not experienced before in life. Circumstance, terminology, and potential interventions are all new, and the personal circumstances of the individual with injury change substantially as a result of the brain injury itself. Both subtle and dramatic changes can be found in a wide variety of areas of function and capability, some of which may be apparent to the individual or family while some will remain to be discovered over time. Some of these changes actually impact the individual's ability to cope, such as difficulties with memory, judgment,

impulsivity, or anger control. Support in crises is important and comes from social structures that involve both family and friends as well as educational and/or work settings. Ironically, in many instances, the availability of these very systems changes as a result of the injury. The result is that crisis, once initiated, is compounded by limitations in coping mechanisms as well as availability of support structures, contributing to a slowed or lesser resolution of crisis.

Crises can include financial, social, medical, and legal matters. In general, it can be very useful to attempt to prepare injured persons and their caregivers by collecting information they may need in the event certain situations arise. The injured person should be provided a succinct medical history that can be conveyed to emergency personnel as needed. Likewise, this information should be provided to health care providers who will continue to care for the injured person upon returning home. A list of past treaters and their contact information can be quite helpful.

The discharge planner should see that discussions have been held with the injured person and the caregivers regarding treatment authorization requirements, advance directives, and durable power of attorney for health care arrangements. Obtaining durable power of attorney agreements can be expensive and, as a result, may not be undertaken. Likewise, guardianship or conservatorship proceedings can be expensive and less likely to be undertaken. Information should be provided to caregivers concerning experienced legal resources within their vicinity and the advantages and disadvantages associated with advance directives, durable power of attorney for health care arrangements, and competency proceedings.

HOME ADAPTATIONS

It is most likely that an individual's home will require some sort of modification to assist in the management of the injured person. Fortunately, there are a number of inexpensive and reliable electronic means to address some difficulties encountered following TBI.

Impairments of smell and taste represent a common area of concern. Smoke, natural gas, and carbon monoxide detectors are available at fairly low cost although, as battery operated devices, they pose a challenge for the memory-impaired in their proper maintenance. Such systems are increasingly available from cable and Internet service provider companies as home security and home monitoring systems.

Caregivers need instruction in establishing a food labeling procedure for storage of food in that spoiled food cannot be detected with impaired smell, taste or, in some cases, vision or judgment. Clearly labeled food containers that indicate a "do not use after" date can be helpful. Cuisinart now manufactures a food container line (SmarTrac™) that utilizes QR codes and an app that enables the user to enter the food type so that the system can associate specific containers with safe expiration dates. The system sends alerts to the user of expired food.

Visual and balance impairments may necessitate the introduction of additional lighting to bedroom, hallway, closet, bathroom, basement, and garage areas, some of which may be enhanced by motion detection capability. Many persons after TBI have balance that relies heavily upon visual input as vestibular and proprioceptive inputs are diminished.[105] Consequently, low-light conditions increase the likelihood of a loss of balance and/or fall, increasing the risk of reinjury.

Accessibility must be considered for the physically challenged individual. This includes access and egress from the living environment and moving around within the environment safely. Access and egress should be considered from the perspective of ramping as well as time required to egress from various areas of the home. Locks on doors may need to be modified so as to allow the person with dexterity problems easy operation in the event of an emergency. Thumb bolt, push button or automatic locks may be helpful. Locks that are code operated may help with problems associated with dexterity or lost keys. It is necessary to consider doorway widths; bathroom fixture access; hot water temperature control; transfer bars or equipment; height and elevation angle of the bed; and placement, height, and sturdiness of furniture. Kitchen safety can be addressed by consideration of electrical disabling of large appliances at the circuit breaker box and placement of a lock on the access door to the circuit breaker box. Stovetops, ideally, should have the controls at the front of the cooking surface. It may be necessary to place nonbreakable dishes in lower cupboards for easier access as well as frequently used foodstuffs.

Persons with oral dysarthria, balance impairments, seizure disorders, or other serious health conditions should be advised to obtain a medical alert bracelet, which will allow public safety officials a means of independent verification of a condition. This can be crucial in obtaining needed medical attention and also in avoiding inappropriate incarceration under the mistaken impression of public intoxication. Additionally, the individual can be given an identification card that indicates the nature of his or her disability and provides contact information for a responsible family member, friend, and professional. This card should also contain a current list of medications and dosing instructions. Emergency personnel in some areas utilize a convention referred to as ICE, which stand for "in case of emergency." The term ICE can be placed in a contact's name in a cell phone directory, or the cell phone can be programmed with emergency information that is accessible without a phone's security code in an emergency. ICE information can also be placed in a vial on a refrigerator where emergency personnel are trained to look for information about emergency contacts, medical conditions, medications, allergies, and so on.

Consideration should be given to the utilization of portable telephone equipment in the home with backup fixed equipment. The portable phone should have an extended-life battery capability and a loud, continuously sounding page/find feature due to memory difficulties that may make finding the portable phone difficult. Placement of multiple

phones should be considered for the physically challenged person. Phones are available with very large buttons for easy dialing for the visually or physically challenged person. Likewise, phones that allow for light indicators for incoming calls and volume adjustments can be useful for the hearing impaired. Last, an easily operated answering machine can be helpful in managing communications along with preprogrammed cellphones.

It is important to consider available telephone service options. Depending upon the individual's needs and status, a landline may be the best option for dependable access. Voice-over-Internet protocol (VoIP) telephone service may require some periodic troubleshooting that may exceed the individual's capability and may be subject to inconsistent Internet availability through the Internet service provider. This option should include emergency 911 coverage. A benefit to these types of services, however, is their low cost. Given budget constraints, these services often allow local and long distance calling at very attractive prices. Traditional phone sets with larger buttons, clearly marked emergency services buttons, and integrated answering machines can be quite helpful. Some services also allow connection to cellular phones while in range. Newer phone systems allow integration with a person's cellphone, enabling its use and/or assisting in locating a lost cell device.

Cellular (smart) phone use may benefit from activation of "find phone" types of services in the event that the cell phone is misplaced. These services can cause the phone to sound continuously to enable easier location, be locked, or be erased although the individual must have access to another cellular device, tablet, or computer to conduct the search. Family members can do so with their devices assuming they have the correct user names and passwords for the individual's accounts. Finally, GPS service activation is required and can be useful in locating an individual who may be out in the community by those providing caregiving services.

Systems are available that allow for telephonic alerts to be delivered in the event of an emergency. The system operates when a remote medallion worn by the user is activated. This can be useful for people with diabetes, balance problems, seizure disorders, etc. The system contacts either a service or a user-defined contact to relay the emergency message.

Bathrooms should be equipped with grab bars around the shower/tub and toilet areas. Hand-held shower wands can be helpful for the physically challenged person. Bath benches that are nonslip and nonslip floor coverings for the shower/tub area and adjacent flooring should be considered. It may be necessary to remove glass shower door fixtures, both for access and safety in the event of a loss of balance. Bowed shower rods and curtains can provide extra space in the shower. Ground fault interrupt electrical receptacles should be installed in the vicinity of water, such as in bathrooms and kitchens, if not already present.

Remote electrical control devices can be helpful in managing the environment. These include remotes for common equipment, such as televisions and radio/stereo units, but can also be purchased to control lighting and other electrical appliances. Such units are referred to as BSR or X-10 units and function by transmission of a signal through existing electrical wiring to specially installed light switches or electrical outlets. More modern systems are available for use in homes with Internet and WiFi availability. These systems can be operated from smartphones or computers and can include security systems as well as remote operation of thermostats, lighting, door locks, and appliances. The system can be operated both by the individual and by other authorized parties.

In general, home evaluations are conducted by occupational and/or physical therapy staff members. These individuals are quite skilled in conducting these evaluations. It can be useful to have a community resource catalog available to caregivers that lists vendors of equipment and services.

Some individuals own weapons and keep these in their living environments. The existence of weapons in the home should be explored and recommendations for their management made. Safety becomes an issue not only for the physically or judgment impaired person but also for the depressed person.

The Internet continues to evolve and offer increased access to services. Shopping for many items can be safely conducted via the Internet, and social contact can likewise be enhanced. Some communities have grocery and pharmacy ordering and delivery available via Internet services. Of course, the Internet is also a place of vulnerability for social and financial matters. E-mail contact with an established list of friends and professionals can be quite useful. Chat rooms can be risky and difficult to use although, if properly managed and monitored, may be a reasonable social outlet. Resources such as useful websites or services, identified in advance for the injured person and the caregiver, can be provided. Families may want to consider the use of certain content filters for the protection of the individual.

FINANCIAL PLANNING

Families need help in preparing for the loss of income often associated with TBI. Osberg et al.[106] reviewed missed work days and financial consequences for parents of traumatically brain-injured children. Table 35.2 shows the percentage of families reporting various problems at 1- and 6-month postdischarge intervals sorted by severity of injury. A high percentage of parents reported a loss of work time and injury-caused financial problems.

In a long-term outcome survey conducted of more than 300 families averaging 7 years postinjury, the mean reduction in monthly earnings for the injured person was more than $1,000 per month in 1997 dollars ($1,482 in 2015).[76] On a family basis, mean monthly income reduction 7 years postinjury was more than $400 ($593), suggesting that other family members had either obtained employment or sought higher wages, perhaps in response to the loss of an income. It should be noted that virtually all persons in this study

Table 35.2 Percentage of families agreeing or strongly agreeing by injury severity score

	Injury severity		
	Mild (*n* = 36)	Moderate (*n* = 30)	Severe (*n* = 14)
1 month postdischarge			
Financial problems			
The injury is causing financial problems***	17	27	79
Additional income is needed**	11	17	50
Work problems			
Time is lost from work	36	47	57
I am cutting down the hours I work*	17	30	57
I stopped working because of child's injury*	3	17	29
6 months postdischarge			
Financial problems			
The injury is causing financial problems**	14	20	57
Additional income is needed**	6	10	43
Work problems			
Time is lost from work**	22	27	71
I am cutting down the hours I work***	0	7	57
I stopped working because of child's injury**	0	10	29

Source: Osberg et al., *Brain Injury*, 11, 1, 11–24, 1997; Taylor & Francis, Ltd. (http://www.tandf.co.uk/journals). With permission.

Note: Examples of how to read this table. Among the 36 children with mild injuries, 17% of families reported the injury is causing financial problems versus 27% among the 30 families of children with moderate injuries and 79% of the 14 families of children with severe injuries. The three asterisks indicate that the percentage differences across the three severity groups are significant at the .001 level.

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

had insurance of one sort or another that provided funding for their rehabilitation. This is important in that some of these individuals were covered by either liability or workers' compensation coverage, both of which are likely to provide some income on a long-term basis. This is obviously not the case for persons without such coverage. The income loss may be markedly higher for people without these coverages.

Families should be encouraged to immediately review their budgets and spending plans. Larger purchases should be reconsidered or postponed. Refinancing, consolidation, or restructuring of family debt may become important. Again, most families are overwhelmed with the changes in their day-to-day reality and will not have considered these long-term issues. The discharge planner may be able to provide a resource list of lenders willing to assist with debt restructuring, refinancing, consumer education, etc. In some instances, families may have other income resources they can call upon to assist with short-term financial needs as they adjust to a lower income as a family unit. These can be found in retirement funds, whole-life insurance policies, and supplemental disability policies. Families may need to consider the sale of certain assets to both generate income and to reduce indebtedness.

The injured individual may have handled day-to-day money management prior to injury. If so, the person may not be able to adequately manage family or personal finances due to cognitive or physical disabilities. It may be necessary to arrange for others to access the individual's banking accounts in order to properly manage finances. Credit card balances should be reviewed along with a full expense analysis to provide for any necessary restructuring of spending and debt servicing. Of course, although a family member may take this responsibility on, some protection for the injured person may be necessary via establishing financial conservatorship.

End-of-life issues are difficult for many families to discuss and plan for, either with or without TBI. Yet the financial consequences of death can be considerable. Estate planning can identify useful tools to assist a family to plan for the death of caregivers. Simple review of a family's likely net worth will determine whether formal tools, such as trusts, might be helpful in reducing tax consequences, asset protection, and preservation of maximal funding for the injured family member. Life insurance policies, both individual and second-to-die policies, may be warranted to help in provision of some funding for care. It can be helpful for parents to discuss their intentions for the use of proceeds from their estate upon their death with noninjured siblings, especially if a decision is made to reserve those proceeds primarily or entirely for the injured family member. As families age, different estate planning approaches may be appropriate. For example, a family with several young children may be inclined to plan estate distributions for the benefit of all the children. However, as children become adults who are providing for themselves, the family may change its direction of estate proceeds to benefit those who are unable to provide for themselves.

Last, the discharge planner should provide information and/or application forms necessary for SSI, SSDI, and/or Financial Aid to Dependent Children.

ADDITIONAL REHABILITATION TIMING

Some persons with TBI recover over a period of time that is fairly concise and confined in duration. Others, however, experience recovery in a less time-contiguous fashion. Still

others may experience a fairly good period of recovery and success following discharge, only to experience postdischarge complications that cause the individual to regress to a lesser level of functioning. A return to rehabilitation services can sometimes be useful in furthering the recovery of an individual or in reestablishing a previously attained level of function. Many studies report functionally significant improvements and reduced disability levels achieved during later application of rehabilitation services after chronic placement in institutional or home settings.[107–117] These studies conclude that, in individuals with moderate-to-severe brain injury, substantial functional and neurobehavioral impairment can be reasonably expected to achieve statistically significant functional improvements following application of "late" rehabilitation. The literature, however, does not provide a thorough review of the characteristics of those persons who respond well to late rehabilitation, at least not enough to provide a clear delineation of that group from one that will not benefit.

The propriety of additional rehabilitation depends upon the reasons for a lack of progress in earlier rehabilitation attempts or the reasons for deterioration from previously achieved levels of functioning. Regression or deterioration observed following brain injury can usually be traced to a medical, psychological/emotional, or environmental etiology. The key is to accurately identify which of these may be active as reasons for a decline in function and determine whether they can be reversed or changed. One example might be the identification of iatrogenic complications associated with inappropriate pharmacological intervention. Another might be a change in a family system in which an undue amount of overdependence was fostered for many years, only to require further intervention when the responsible family member or caregiver is no longer available or able to provide care. This might occur in the sudden death of a parent or a decline in health of a caregiver due to advancing age. Again, regularly scheduled follow-up contact may allow identification of such situations and allow the discharge planner to proactively advocate for additional rehabilitative services.

SUMMARY

The world of health care has changed tremendously in the last two decades and, alarmingly, more so in the last few years. Shorter LOS and decreasing financial resources have increased the level of acuity with which people are discharged from treatment settings and level of disability with which people are returned to home environments. Ongoing care and treatment is relegated, many times, to the injured person and his or her caregivers. The burden for discharge planning cannot fall to a single individual on a treatment team, but rather must be dealt with by the entire team and, institutionally, by the resources developed and made available by the treating facility. Whether viewed as a part of patient care, advocacy, or community service, the creation of resource and information centers provides a vital service to persons with TBI and their families. Caregivers must be encouraged to maintain contact with previous care providers and to actively manage and participate in follow-up activities.

The responsibilities carried by discharge planners are immense, and the information suggested herein materially adds to an already overwhelming workload. A checklist is provided in Appendix 35-B to assist the discharge planner in both approaching and organizing a discharge for a person with TBI and as an outline for services that the discharge planner might encourage to be developed, institutionally, to support excellence in discharge planning.

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APPENDIX 35-A: FAMILY MANUAL OUTLINE FORM

Name:
Date of birth:
Date of injury:
Injury *(in layman's terms):*
Location of injury:
General approach:

Discuss 1) what has been used in therapy for ADL completion, 2) what to expect that the individual needs for assistance, 3) specific areas of deficit and how they affect performance, 4) behaviors exhibited, and 5) what tasks are priority and must be completed and which should be encouraged.

Behavior:

Make note of all behaviors, including but not limited to physical aggression, angry language, exiting, stealing, self-abuse, nonparticipation, sexually aberrant behavior, and property abuse. This section should also include how to provide reinforcement and what approach to use to gain participation and compliance.

Ambulation status:

Include level of independence with ambulation, what type of assistive device is needed, and the type of supervision required.

Speech:
Vision:
Adaptive equipment:
Activities of daily living:

A. Hygiene and grooming *(include information on showering ability, oral care, combing hair, make-up, etc., with how much assistance needed)*
B. Dressing *(include how much assistance is needed and any adaptive equipment)*
C. Toileting *(note level of independence, including limitations)*
D. Medication *(who should be responsible, times, any special instructions)*
E. Meal preparation *(include level of assistance needed for all meals)*
F. Eating *(include level of help needed, type of diet, any special dietary needs or restrictions)*
G. Bedtime/wake-up/alarm clock *(structure should be maintained as much as possible to maintain abilities; include techniques used to gain compliance)*
H. Laundry *(how often and what assistance is needed)*
I. Dishes *(note assistance level needed)*
J. Mail retrieval, if appropriate
K. Time management *(note level of ability)*
L. Travel *(include how the individual will be transported with level of assistance needed)*
M. Grocery shopping *(list help needed for shopping list, money, food storage, etc.)*
N. Money management *(note level of involvement and who is responsible)*

Outings/leisure activities:

Include type of activities the individual enjoys and can participate in. Set expectations for the outing if behavior exists.

Daily routine

Outline a typical day for weekdays and weekends, including any help needed, such as a checklist.

Vocational/avocational involvement

Include responsible parties, level of participation, supervision needed, etc.

Nursing/medical issues

Include current medications, any specific care issues or restrictions, allergies, etc.

Therapeutic home programs

List activities from the therapists that the person can do at home. Outline the goal and procedure for the activity using pictures, videos, etc.

APPENDIX 35-B: DISCHARGE PLANNING CHECKLIST

Name: _____ Date of estimated discharge: _____
Guardian/conservator: _____ Discharge address: _____
_____
_____
_____
Financial/power of attorney: _____

1) Living accommodations:
   A) Apt. _____ Home _____ Rented _____ CNS innovations ____
      Owned _____ Group home/assisted living _____
      Other _____
   B) Cleaning needs:
      1) Self or family _____
      2) Outside agency _____
   C) Home modification needs/considerations:
      Home assessment needed: Yes _____ No _____
      1) Lighting needs: _____
      2) Door locks: _____
      3) Bathroom fixtures: _____
      4) Hot water temperature control: _____
      5) Doorway widths: _____
      6) Ramps: _____
      7) Transfer bars: _____
      8) Stove top controls: _____
      9) Ground fault interrupt electrical receptors: _____
      10) Remote electrical controls: _____
      11) Shower:
         a) Roll-in shower
         b) Hand-held wand
         c) Grab bars
         d) Bath bench
         e) Shower chair
      12) Alarms:
         a) Smoke alarm
         b) CO_2 detector
         c) Natural gas detector
         d) Home security system
      13) Room accessibility:
         a) Furniture placement
         b) Nonskid rugs
         c) Carpet pile
      14) Other: _____
      _____
      _____
   D) Equipment needs:
      1) Resource catalog/vendors
      2) Answering machine/emergency response system
      3) Specialized vehicle
      Type: a) Automobile
      b) Van
      c) Electric scooter
      Maintenance: _____

4) Wheelchair type: _____
   Maintenance: _____
   Special modifications: _____
   Own or rent: _____
5) Walker type: _____
   Maintenance: _____
   Special modifications: _____
   Own or rent:_____
6) Cane type: _____
7) Other: _____
   _____

a) ADL equipment
   1) Grooming/hygiene: _____
   2) Dressing/cooking: _____
   3) Recreational: _____
   4) Ergonomics: _____

b) Orthotics
   1) Splints: _____
   2) AFO: _____
   3) Slings: _____
   4) Other: _____

E) Supplies: *Identify supplies that will be needed on an ongoing basis.*
   1) Incontinence supplies: _____
      _____
   2) Feeding supplies: _____
      _____
   3) Eyeglasses: _____
      _____
   4) Medical identification bracelet: _____
      _____
   5) Other: _____
      _____
      _____
      _____

2) Supervision/caregiver needs
   A) Hours required

	Weekday	Weekend
1) a.m.	_____	_____
2) p.m.	_____	_____
3) O/N	_____	_____

   B) Type
      1) Family _____
      2) Agency _____
      3) Nursing _____
   C) Respite alternatives: _____
      _____
      _____
   D) Responsible party postdischarge: _____
      _____
      _____
   E) Recommended daily structure: _____
      _____
   F) Caregiver manual that is patient-specific with anticipated complications. (see attached outline.)

3) Community resource analysis:
   A) School options: _____
   B) Work options
      1) Volunteer
      2) Day treatment
      3) Sheltered employment
      4) Competitive employment
      5) Department of rehabilitation
   C) Transportation: _____
   D) Shopping: _____
   E) Hospitals/urgent care/emergency services
   F) Banks: _____
   G) Religious information: _____

4) Medical:
   A) Medical history: (*Include medical precautions and concerns as well as past treaters with contact.*)
   _____
   _____
   _____
   _____
   _____
   _____
   _____
   B) Physicians:
      1) Primary physician: _____
      _____
      _____
      2) Physiatry: _____
      _____
      _____
      3) Neurology: _____
      _____
      _____
      4) Psychology: _____
      _____
      _____
      5) Orthopedic: _____
      _____
      _____
      6) Ophthalmology: _____
      _____
      _____
      7) Dental: _____
      _____
      _____
      8) Other: _____
      _____
      _____
   C) Therapy: (*days/hours*)
      PT _____ OT _____ SP _____ Counseling _____ Job coach _____
      Location: _____
      _____
      _____

Prescription obtained: Yes/no _____

D) Medications:

Name Pharmacy Physician

_____

_____

_____

_____

_____

Known allergies: _____

Seizure history: yes/no _____ Date of last seizure: _____

E) Dietary recommendations: _____

_____

_____

F) Swallowing precautions: _____

G) Restrictions:

1) Driving _____
2) Bicycles _____
3) Heights _____
4) Lifting _____
5) Power equipment _____
6) Standing/sitting _____
7) Chemical/hazardous materials _____
8) Working overhead _____
9) Sport participation _____
10) Other: _____

_____

_____

5) Behavior:

A) Type:

Physical _____

_____

Cognitive _____

B) Plan and expectations: _____

_____

C) Crisis plan: _____

_____

6) Individual/family education: *Provide information in the following arenas:*

A) Seizures
B) Drug interactions
C) Long-term effects of TBI
   1) Second impact syndrome
   2) Depression
   3) Alcohol/drug
   4) Sleep hygiene
   5) Hydration
   6) Bowel/bladder
   7) Reinjury
   8) Aging issues
D) Community support systems
E) Treatment authorizations
   1) Advanced directives
   2) Durable power of attorney for health care

F) Therapeutic home programs
G) Guardianship/conservatorship, if needed
H) Public assistance, if needed
I) Behavior interaction/approach
J) Allergies
K) Emergency preparedness
    1) Emergency care
L) Sexuality
M) Social skills development
N) Safety issues related to delivery of care and site of delivery

7) Financial planning:
A) Family budget review
    1) Restructure debt
    2) Use of retirement, life insurance for short-term needs
B) Public assistance
    1) SSI
    2) SSDI
    3) Medicaid/Medicare
    4) State-specific benefits, i.e., victims of violent crimes, regional center, low-income housing, disabled phone and electric rates, Easter Seals, CCS, service organizations

8) Additional recommendations:

_____
_____
_____

Completed by: _____ Date: _____
Person treated signature/reviewed with: _____
Print name: _____ Date: _____

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Patients' rights and responsibilities, health care reform, and telehealth: Ethical considerations

THOMAS R. KERKHOFF AND STEPHANIE L. HANSON

INTRODUCTION

Ethical dilemmas are a bit like an artist's brush strokes—no two are exactly alike, yet there are consistent fundamentals underlying each one, eventually coalescing into a coherent image. Ethics codes provide the fundamentals for decision making, but like the artist, the health care provider uniquely applies color, texture, and perceptual form to the paper or canvas differently each time. Patients and families interact with health care providers in unique ways to create the complexities surrounding ethical issues that necessitate ethical decision making and ultimately case resolution. In this chapter, we return to where we began in the first edition of this text: understanding how ethical principles and operationalized standards get played out in the health care environment. First, we describe the moral fabric that is ethics, and, then, we focus this chapter on one of the most straightforward yet complicated concepts in contemporary health care: the principle of respect for autonomy. We overview a primary concept that illustrates this principle, the patient's fundamental right to self-determination. The discussion then branches into the realm of current issues with a discussion of ethical considerations (primarily founded in distributive justice) bound to the ongoing debate regarding health care reform and the Patient Protection and Affordable Care Act.[1] Finally, we will concretely discuss the acquisition of informed consent in the burgeoning area of telehealth.

ETHICAL FOUNDATIONS

The fundamental tenets of bioethics provide the health care practitioner, independent of discipline or specialty, with operationalized moral concepts applied to the process of providing health care services.[2] The principles of bioethics and the practice standards detailed in the varied ethics codes formulated by each health care professional discipline must be validated within the personal and social contexts of the person(s) served in order to achieve relevancy in daily life.[3] It is in the consistent application of bioethical principles and attendant practice standards in the course of everyday practice that health care providers ensure quality services to those persons we serve. An argument that the authors have made across the past decade[4,5] is that the social perception of codes of ethics existing solely as a set of criteria dictating sanctions to be applied when practice errors occur is false. Rather, ethical principles framing codes of ethics underpin every professional action taken in the context of care provision. Consistent and universal application of bioethical principles is the sine qua non for best practices among individual practitioners, professional disciplines, and health care organizations alike.

Of the four ethical principles laid out by Beauchamp and Childress[2]—respect for autonomy, beneficence, nonmaleficence, and justice—respect for autonomy is rife with complex challenges related to health conditions and situational factors that can constrain the right to choose and exercise control over one's person. In the context of traumatic brain injury, compromised cognition offers a dramatic example of constraints imposed upon autonomy by a health condition. Varying severity of cognitive and physical impairment along the recovery trajectory requires that both health care providers and family members/social support systems interacting with the survivor be aware of the person's cognitive processing and physical performance capacities, offering appropriate

supports and accommodations as instances demanding decisions arise. Likewise, the principle of justice pertains to the broader social issues of access to and availability of health care resources adequate to meet the ongoing needs of survivors of TBI. In addition to autonomy and justice, beneficence (preventing harm or facilitating good) figures prominently in strategic and tactical decisions regarding promoting, implementing, and regulating telehealth services. All of these principles underpin the discussions to follow.

PATIENT RIGHTS AND RESPONSIBILITIES

Understanding one's rights and responsibilities as patients in a health care system offers an illustration of the challenges that must be addressed in provision of ethical health care to individuals who have survived traumatic brain injury. Pozgar[6] outlines varied patient rights and responsibilities listed here. The reader is encouraged to envision how each of these basic rights and responsibilities can be fostered and protected for the person(s) served in the context of the treatment environment in which services are provided. The question is posed, "What can I proactively do, in partnership with the health care organization to which I am allied, to protect and honor patient rights and facilitate patients' assuming responsibility for their care?"

Patient Rights

1. Right to know one's rights
2. Right to explanation of one's rights
3. Right to know hospital's adverse events
4. Right to admission
5. Right to quality care
6. Right to participate in care decisions
7. Right to informed consent
8. Right to privacy and confidentiality
9. Right to refuse treatment
10. Right to execute advance directives
11. Right to designate a decision maker
12. Right to know restrictions on rights
13. Right to have special needs addressed
14. Right to emergency care
15. Right to discharge
16. Right to transfer
17. Right to access medical records
18. Right to know third-party care relationships
19. Right to know caregivers
20. Right to sensitive and compassionate care
21. Right to respect
22. Right to a timely response to care needs
23. Right to pain management

Patient Responsibilities

1. Recognizing the effect of lifestyle on one's health
2. Keeping appointments
3. Providing caregivers truthful and pertinent information
4. Engaging in a healthy lifestyle—exercise, diet, positive social relationships
5. Providing caregivers with timely, accurate, and complete health information
6. Asking questions and seeking clarification about a plan of care
7. Seeking a second opinion when in doubt
8. Describing location, severity, and treatment options for pain management
9. Describing previous treatment options utilized—successful and failed
10. Alerting caregivers to medication allergies/unacceptable side effects
11. Maintaining a record of medication effects
12. Following an organization's rules and regulations
13. Complying with a treatment plan
14. Accepting responsibility for consequences of refusing treatment or not following instructions
15. Being considerate and respectful of the rights of others
16. Being respectful of the property of others
17. Alerting staff as to preferences in care
18. Understanding caregiver instructions
19. Reporting fraudulent activities that contribute to raising health care costs

As can be gleaned from the above information, provision of health care requires active personal investment in the process of care provision. Not only must the ethical health care provider and health care organization respect and facilitate the ensuring of patient rights, but the patient must also shoulder responsibility for receiving safe, efficient, effective, quality care through reciprocal cooperation. Careful reading of the rights and responsibilities highlights the potential for ethical challenges, given the effects of the person's health condition (in this case, traumatic brain injury) upon thinking and behavior, the wide variety of personal and social values and beliefs regarding health care, and the social role expectations developed during varied life experiences prior to injury, etc. Questions such as the following inevitably arise: "How can health care providers and organizations hope to ensure respect for patient rights when the most basic cognitive abilities governing understanding and behavior have been compromised by brain injury?"

In the past, paternalistic protection was often the response of well-intentioned providers. Based upon the erroneous assumption that any compromise of cognitive or emotional processing incapacitated the patient, decision-making was performed by the "expert" health care provider who functioned under the ethical concept of considering the patient's "best interests." However, as research into the complexities of cognitive and emotional processing during recovery from brain trauma revealed a mix of preserved and variably impaired functional reasoning subsystems operating in a dynamic manner during recovery, consideration of cognitive impairment after brain injury as being global was dismissed.[7–10] In a parallel vein, academic exploration of

evolving ethical thought regarding the principle of respect for autonomy focused upon the concept of "substituted judgment" (i.e., what would the patient do or want) as the gold standard for ethical decision making.[2,11]

Let us explore the implications of patient rights and responsibilities under the principle of respect for autonomy in more detail. We can begin by making some fundamental assumptions regarding the functional capacities required of a reciprocity-based relationship between a patient and the health care system. These nonexhaustive assumptions regarding patient rights may include 1) autonomous personhood; 2) the ability to communicate values, beliefs, preferences, and expectations regarding a proposed treatment plan; 3) understanding of what is owed to a patient by the health care system; and 4) trust in the health care system to respect patient rights. Likewise, assumptions regarding patient responsibilities can be described as 1) autonomous personhood 2) ability to understand what is required of a patient in a health care context, 3) intention to cooperate with the efforts of the health care team in executing a treatment plan, and 4) intention toward self-advocacy in service of meeting personal needs in health care and social contexts.

Regarding patient rights, assuming autonomous personhood in a situation of recovery from TBI requires a value judgment on the part of the health care provider. Understanding the cognitive–behavioral complexities of recovery from such an injury is only the starting point. Ongoing comprehensive assessment of ever-changing cognitive capacities and communication of these data to the treatment team are integral to making accurate judgments about decisional capacities at any point in time. Frequently, updated assessment data dictate the degree to which a patient can participate in decision making and the kinds of accommodations that may be required to optimize that participation.

Although communication ability is impaired in some individuals with brain injury, the ability to indicate (in whatever manner is practical) information reflective of one's personal value system provides the contextual backdrop against which a treatment plan can be formulated. Such an approach to treatment plan development offers relevancy for the individual and can increase the likelihood of cooperative buy-in and outcome benefit. However, this process of facilitating communication of person-relevant expectancies can be laborious and time-consuming if significant communication impairments are present. Involvement of family perspectives on the patient in such circumstances can hasten the uncovering of personal values, beliefs, and preferences; life experiences; and personal goals present prior to injury. At times, such personally relevant information can only be ascertained from behavioral responses to performance tasks during the process of treatment. Observational data regarding behavioral responses to treatment plan activities is a valuable assessment tool in such situations.

Ascertaining what a person understands regarding what is owed to her or him as a patient falls under the concept of personal preferences and expectations. Again, obtaining such information early in the development of a treatment plan can lead to emphasizing person-relevant values, increasing the likelihood of active participation in treatment. At the same time, misconceptions about what is owed to a patient by the health care system can be addressed. Such "reality checks" are invaluable in helping the patient to tailor expectations about what possibilities exist regarding goal achievement within any treatment plan. For example, a patient with a severe injury voicing an expectation that the rehabilitation program will result in complete recovery (return to preinjury functional status) offers the treatment team the opportunity to help the person understand recovery, strengths and weaknesses, and how to evaluate the rate of recovery via individualized performance metrics applied during treatment in a realistic manner while simultaneously maintaining a positive perspective regarding hope. Similarly, these checks help the rehabilitation team ensure they are investing their time and experience in a plan that will facilitate trust, build patient engagement, and, ultimately, support positive outcomes.

Trust is earned and cannot be presumed present via the reputation of the program, professional status, or other personal characteristics of the provider. During acute care, and often early in a rehabilitation admission, a patient with a clinically significant brain injury can be considered "essentially dependent" upon the health care team for sustaining basic life functions, including health and safety.[12] However, as recovery progresses, this dependency gradually diminishes and is replaced by a return to preinjury or modified preferences and expectancies as awareness of self reemerges. Thus, a cooperative patient early in an admission may become less cooperative as comparative thinking comes online—evaluating current performance against preinjury performance criteria in similar tasks. Patient trust in the members of the treatment team when such incongruent realization occurs is based upon consistency of intervention, accuracy in communication, and maintenance of a supportive mindset in social interaction with the patient across the admission. The adaptive rehabilitation approach to accommodating disability—developing practical strategies and tactics to accommodate challenges in everyday living and mobility in a social atmosphere of "can do" support—is a consistent given in the process of patients adjusting to the new reality of their capabilities. It is in this consistent attention to and advocacy for the patient that trust arises and is repeatedly reinforced.

Considering patient responsibilities, assuming autonomous personhood is the primary conception. The patient's awareness of the value of cooperation with the treating professionals requires an accurate sense of self in the context of health compromise and diminished cognitive and physical performance capability. Whereas, prior to injury, encountering tasks akin to those found in the treatment setting could have been achieved with ease, performance requirements of the current treatment plan may require seemingly super-human effort, entail experiencing significant pain

and may end in performance results that fall significantly below preinjury baseline expectations. A decision on the part of the patient to actively participate, openly communicate treatment-relevant information, and adaptively alter lifestyle expectations to accommodate disability marks a Herculean change in self-identity and expectations for the future. Facilitating accurate self-definition in light of disability is a critical role for every member of the treatment team. The patient's reattaining an acceptable and meaningful degree of autonomy in the form of control over daily choices and future planning, even with limitations, is central to the process of rehabilitation.

Understanding what is expected of a patient demands that the treatment team operationalize cooperation in the context of daily performance requirements of the treatment program. This conceptually complicated idea can be brought into practical focus by repeatedly demonstrating program expectations via daily treatment tasks, reinforcing the previous treatment session's performance outcome for the patient in comparison with current task accomplishments. Incremental improvement is the reality even when those increments are measured in minute units. Additionally, selectively reinforcing cooperative, effortful patient responses to treatment tasks across days facilitates self-understanding of the patient's critical active role in the treatment process. When the patient spontaneously generalizes task performance from the treatment environment to a nontreatment environment or situation, at least limited understanding can be inferred.

As the treatment process continues, it is hoped that the health care team will observe a diminishing level of cueing and direction required to secure patient participation in treatment. A predictable daily and weekly activity schedule and the continual building of increasingly complex behavioral responses upon previous performance achievements within the treatment plan offers the patient a level of cognitive and emotional comfort that can foster development of intentioned participation in the rehabilitation process. The realization that the right of treatment refusal may result in diminished performance outcomes and more limited functional recovery can offer the patient a confidence-based position upon which to opt for active participation in treatment.

Further behavioral evidence of increasing self-awareness of one's autonomy can be seen in spontaneous patient advocacy with the team and other stakeholders for meeting immediate and future personal needs. It is this realization of and taking on personal responsibility for navigating the sometimes unpredictable currents of everyday community living that increases the possibility of successful adjustment to one's postinjury capacities and limitations. To the extent that rehabilitation can simulate such decision points during treatment, the patient's experience base with such tasks increases. In time, recognition of Dunn's[13] broadened concept of disability as a societal challenge becomes an integral part of the person's life trajectory, demanding self-advocacy in service of achieving a level playing field regarding the rights of individuals to succeed within our social framework.

Taking the broadening aspect of disability and personal–civil–human rights even further, there has been an international emphasis in the policy literature in recent years embodied in the World Health Organization's Disability and Rehabilitation Action Plan 2006–2011[14] and in the United Nations Convention on the Rights of Persons with Disabilities.[15] Basic human rights of persons with disabilities are rooted not only in respect for autonomy, but also find grounding in the ethical principle of justice (exemplified in the concepts of equity in access to health care and equal opportunity regarding the goods of life). It is increasingly recognized that disability is a social phenomenon that requires action in crafting adaptive social policy in support of community-based service delivery; applying adaptive technology resources; providing increased health and rehabilitation resources; and networking support resources throughout one's life span within communities, states, and at the national level. It is equally evident that application of the current medical insurance short-term and cure-oriented funding model to individuals with lifelong disabling conditions falls short of meeting the ongoing support needs of people living with disabilities. Our social fabric requires a new weave that integrates lifelong adaptive support for individuals with disabling conditions within elemental building blocks of society; for example, providing effective and efficient infrastructure for health, safety, sanitation, energy, etc.

HEALTH CARE REFORM: THE DEBATE CONTINUES

Lachman[16] framed a portion of the ethical argument linked to health care reform when she asked, "Can Americans continue to allow the self-protective practices of insurance companies in excluding high-risk individuals (e.g., preexisting conditions, lifetime caps on benefits)? The principle of Autonomy was never meant to abandon the moral relationships that continue to be necessary for the human good."[16] When we consider the lifetime cost of allocating adequate resources to support the health and well-being of survivors of traumatic brain injury, we come to the crux of the matter. Lachman[16] presents two possible ethical views that cast conflicting light on access to health care and its economic costs. She divides the two philosophical camps into liberal egalitarians and libertarian/free market advocates. Liberal egalitarians espouse that 1) health care is a fundamental good, and access to this good allows us to become full members of society; 2) a right to health care must be exercised by removing all barriers to access; 3) justice, equality, and community solidarity are values; 4) health care is a right; and 5) a single-payer system is the solution. Contrasted with that perspective, libertarians hold that 1) the role of government is protecting the freedom of all persons to choose their own goals and means to pursue them, 2) people have the right to (governmental) noninterference, 3) freedom and personal responsibility are values, 4) health care is a commodity, and

5) decentralized market mechanisms with personal payment are the solution.[16] The ongoing political furor over the PPACA appears to be captured in these contrasting views of providing health care in the United States. Interestingly, as the PPACA is currently formulated, it combines aspects of both of these contrasting positions.[1]

During early development of the PPACA, there was consideration of a single-payer system as an alternative to the business-oriented medical insurance model that had held sway. That provision was dropped from the final bill, leaving an outcomes-incentivized free market to define economic support mechanisms for provision of health care services with some caveats (see an exposition of myths surrounding the roll-out of the PPACA).[17] Still, the PPACA is a step toward universal public health care, inching toward an implied right to basic health care[18] despite lack of health care as a defined right in either the U.S. Constitution or Bill of Rights. Interestingly, as of this writing, there is a U.S. House of Representatives resolution[19] that endorses expanding Medicare to cover everyone, functioning as a single-payer health insurance program, and citing significant savings in administrative costs as one rationale for support. Likelihood of passage into law is dubious given the current makeup of Congress, but it represents the fact that an equity-based approach to health care is still under consideration by policy makers.

Constructively, some patient protections were folded into the PPACA—creation of state-managed insurance exchanges (or federally managed if states refused government subsidies to expand Medicaid), offering a choice among affordable insurance plans for those persons meeting economic eligibility criteria; removing the barrier of preexisting conditions that limited insurability; and emphasis on quality measures, for example, interprofessional treatment team-based service delivery, evidence-based practice, developing metrics for evaluating and incentives for producing positive patient outcomes and sanctions for failure to comply, creation of patient care homes, parity between physical and mental health conditions, preventive services, and support for wellness programs.[20] Nonetheless, political infighting has complicated full implementation of the law with significant variability across state statutes regarding its effect upon actual health service delivery systems. Pending the outcome of political wrangling, the full implementation and transformation of the U.S. health care system won't likely be realized for a decade or more—see the final portion of this discussion for an update on health care reform since the 2016 election.

On the other hand, providers and health care organizations have responded adaptively to the passage of the PPACA by creating new infrastructure in the adoption of electronic medical record systems that can communicate more effectively across health service delivery settings, restructuring practices into multi-disciplinary integrated care organizations, and wholesale adoption of the interprofessional team treatment model—the hallmark of rehabilitation since its inception. Indeed, Wynia, Kishore, and Belar take the ethical position regarding an integrated national health care system a step further in proposing a "transdisciplinary code of ethics,"[21] spanning the spectrum of health-related professional disciplines. Such a code would reflect a new unified social contract regarding the roles and obligations of all health care providers. This moral imperative, if implemented, would help to move the health care delivery system a critical distance from the political arena, placing responsibility for quality care back into the hands of the health care providers with the patient-centered perspective in the spotlight.

In accord with the authors' commitment to the application of ethical principles, we must refocus our attention toward the implications of the PPACA for survivors of traumatic brain injury and their family members. It is the personal impact of new legislation upon the lives of individuals that offers validation of any law. Given the nascent nature of the law's implementation, we put forth several tentative effects that consumers may experience regarding the PPACA. First, formalizing the adoption of the interprofessional team approach into the health care system should enhance transition into the community and the broader social environment after completing rehabilitation. Armed with support from varied health care professionals connected with the patient care home model, primary care providers should be able to deal more comprehensively with the complexities surrounding postacute brain injury recovery from both a medical and psychosocial perspective. This availability of multiple health care disciplines should also be bolstered by the newly defined parity between physical and emotional conditions—often comingled in the survivors of traumatic brain injury. Securing needed services of medical, psychological, social, and community support personnel should prove more seamless within the new integrated health system. This integrated care concept is intended to centralize a wide array of health services around a primary care hub or patient care home. Whether this model reaches an optimal level of effectiveness, especially in rural areas, remains to be demonstrated in outcome data. Implications for rural postacute care will be addressed in the telehealth discusssion to follow.

Second, the PPACA should make access to affordable medical insurance a reality once insurance exchanges are firmly established and market forces are brought to bear under the watchful eye of federal government oversight. However, past profitable business practices typically submit to global change slowly, leaving room for strategic maneuvering and the continual search for loopholes in the law. Early in the process of transition to integrated care, the consumer needs to be vigilant regarding "carving out" psychological services—thereby violating the parity concept written into the law—or capping insurance benefits at lifetime dollar amounts that clearly do not meet the ongoing needs of survivors. The self-advocacy responsibility of patients and families comes to bear in this instance along with patience and persistence. By alerting your health care providers and legislators to problems with access to insurance and health services or undue restrictions in benefits,

weaknesses in the law can be discovered and, it is hoped, mended.

Finally, the challenge of politically motivated refusal of federal funds for the expansion of Medicaid services in certain states, thereby limiting the scope of medical and psychosocial services for survivors, needs to be closely monitored. The survivors of traumatic brain injury are an ideal population to test the ability of the health care system to provide both access to and appropriate health services/supports to meet their legitimate needs. The reason to test the system is that survivors are faced with not only ongoing medical and health challenges, but also psychosocial barriers to full reintegration into local communities. Pressures upon families to provide needed support without access to or availability of psychosocial supports across the life span are enhanced in traumatic brain injury, especially for those survivors of moderate and severe injuries. These individuals and their families will serve as the bellwethers for validating the intent and the practical reality of the PPACA. In this instance, national organizations such as the Brain Injury Association of America (BIAA) may prove invaluable in tracking statistical outcome data across the various states. The prospect of adding not-for-profit organizations, such as BIAA, to the host of agencies and watchdog groups evaluating health outcomes is enticing. This is especially so for survivors of traumatic brain injury because patient and family-centered organizations, such as the BIAA, have intimate knowledge of the panoply of needs required for full community reintegration.

As of this writing, the above ethical issues regarding the politically troubled implementation of the PPACA remain pertinent to the current state of transition as a Republican response (the American Health Care Act) to health care reform is in the early stages of formulation since the election of 2016. The American Health Care Act, proposed in the House of Representatives and currently in committee, includes a number of changes from the PPACA. Such as the following:[22]

- No individual or employer health insurance mandate.
- Insurers can impose a 30% surcharge on consumers with a lapse in coverage.
- Age (not income)-based refundable tax credits for insurance premiums; phased out for individuals with higher incomes.
- No tax credits for out-of-pocket expenses.
- Medicaid—Federal funds granted to states based on a capped, per-capita basis starting in 2020; states can choose to expand Medicaid eligibility, but would receive less federal support for those additional persons.
- Insurers can charge older customers up to five times as much as younger customers.
- Individuals can put $6,550 and families can put $13,100 per year into a tax-free Health Savings Account to pay for health care services.
- High-cost employer insurance plans subject to a "Cadillac Tax" starting 2025.
- Repeal of both the 3.8% tax on investment income, and the 0.9% tax on individuals with incomes above $200,000 and families with incomes above $250,000.
- Private health insurance plans required to offer the same 10 essential health benefits as the PPACA, while some Medicaid plans are not required to offer mental health and substance abuse benefits.
- Insurers banned from denying coverage for pre-existing conditions.
- Dependents can stay on parents' health insurance plans until age 26.
- Insurers prohibited from setting annual and lifetime benefit limits on individual coverage.

We have witnessed several health care insurance companies opting out of PPACA because of insufficient profit generation in the past two years. Such decisions should not only simply rest with normal business performance expectations, but must also incorporate moral reasoning related to the consequences of funding withdrawal and reduced health care service provision upon individuals' health status. The argument that insurance companies have traditionally made to such issues—we do not dictate health care, but only control funding—is specious because of the clear link between funding availability and service provision in the U.S. health care system. Without morally-based financial underpinning, charity care must shoulder the burden in provision of health care to the disadvantaged segments of the population who are effectively denied access secondary to financial barriers. The proposed Medicaid and insurance provisions (if implemented as stated above) would ultimately reduce the number of individuals with affordable access to health care by 15–20 million across the next decade.[23]

While this proposed plan has not yet been voted upon by Congress, it represents a partial reversal of health care reforms geared toward increasing patient protections and affordable accessibility embodied in the PPACA. Making health care a contentious perennial political issue, rather than one of basic infrastructure (as we have traditionally considered sanitation, power, water, roads/bridges, etc.), deflects public attention from the consideration of a decent minimum of health care for all citizens as a basic human right—a policy stance that has been successfully adopted by every other industrialized country in the world. The political wrangling has also moved the United States farther away from adopting a universal (single-payer) health care system that marks the delivery systems of those other countries. Additionally, the removal of the individual health insurance mandate as recommended in the AHCA proposal jeopardizes the ability to provide universal coverage (i.e., as healthier individuals purchasing health insurance are critical to ensuring stability in the overall health care system). Reliance upon a private corporate health care financing mechanism geared toward profit-taking for a significant segment of the population represents a potential moral conflict of interest.[24,25]

While everyday operations of health care organizations can be effectively managed by proven business methodologies, the for-profit model adopted by the private US health insurance sector and some health providers conflicts with provision of cost-effective health care to all U.S. citizens. The portion of every dollar earmarked to support provision of health care services that is diverted toward profit for insurance industry investors, or to corporate profit and executive/employee bonuses, removes that amount of financial support for the health care delivery process. To the extent that economic prosperity in any corporate endeavor is defined by stable, or better yet, gradually increasing profit generation across time, health care insurance premiums and for-profit health care organization charges must necessarily rise, along with the rates/categories of reimbursement denials for services provided. While a rise in health care costs can be attributed in part to cost increases in delivery of health care services (salaries, technology, infrastructure, etc.), rising costs can also be attributed to diversion of health care dollars to corporate and investor profit. The former can be managed to some extent by application of efficiency and effectiveness measures, but the latter cannot be limited because of the continuing profitability expectations inherent in the for-profit business model. Federal cost-containment measures do not apply to private sector businesses outside bilateral contractual agreements.

While we do not know the ultimate content of the latest health care reform law at this time, we can assume that the political party currently in power will require incorporation of many of the changes listed above, ensuring that the cycle of contention between progressive vs conservative ideologies regarding the U.S. health care system will continue into the future.

CHALLENGES AND OPPORTUNITIES OF TELEHEALTH

As the quality and capacity of digital electronic transmission have advanced, the challenges and opportunities in the area of telehealth have been rapidly expanding across diverse health professions. However, there is limited regulation and a lack of consensus on critical components and definitions. In addition, a number of ethical issues challenge this broad area of health service, and these must be recognized and managed in order to ensure the ultimate protection and welfare of the consumer. In this section of the chapter, we offer definitional examples and address some of the ethical issues that working in telehealth presents.

Telehealth is operationalized in a variety of different ways, and its definitions range from parsimonious to comprehensive. For example, in its 50-state review of telepsychology, the American Psychological Association (APA) reported Kentucky's regulatory definition of telehealth as "the use of audio, video, or other electronic means to deliver health care"[26] whereas Texas' definition of telehealth included "the use of advanced telecommunications technology, other than phone or fax, including: (a) compressed digital interactive video, audio, or data transmission; (b) clinical data transmission using computer imaging by way of still-image capture and store and forward; and (c) other technology that facilitates access to health care services or medical specialty expertise."[26] In total, 11 states (Arizona, California, Delaware, Georgia, Idaho, Kentucky, New Hampshire, Ohio, Oklahoma, Texas, and Vermont) were identified as including telehealth, telemedicine, telepsychology, or telepractice in their state statutes or regulations. In that same report, although not necessarily in their statutes, the APA identified several states that offered definitional criteria largely related to mandates for insurance coverage. Some of these states included both synchronous and asynchronous activities (e.g., Montana), and others included only real-time activities for specific services, such as consultation (e.g., Mississippi). Similarly, some states included email and telephone (e.g., Delaware), and others did not, particularly if the email was unsecured (e.g., Georgia).

Despite the fact that Baker and Bufka[27] point out that the telephone is one of the most commonly used vehicles for telehealth services, it is a component of telehealth delivery that remains largely unregulated. Of the 22 states that offered some type of mandate for telehealth coverage, approximately one half clearly excluded coverage for fax, unsecured email, and/or audio-only telephone (Hawaii, Kentucky, Louisiana, Maine, Maryland, Massachusetts, Mississippi, Montana, New Hampshire, Vermont, and Virginia). Overall, although there is definitional overlap, there does not yet exist a consensus regarding core definitional components, which will require increased sensitivity to patient and family understanding, collaboration across disciplines who conceptualize telehealth differently, and insurance regulation. Although the reimbursement challenges warrant significant consideration, these will have to wait for another chapter. The focus of this section is on the rich ethical minefield that arises within the burgeoning telehealth field, which we explore primarily in the context of the ethical principles of respect for autonomy, beneficence, and justice (specifically related to access to services).

The overarching goal of telehealth, variously defined, is similar to health care delivery in general: to facilitate optimal health and/or quality of life. Fundamentally, as ethical health care providers, we want to facilitate good (by making decisions that benefit our patients), prevent harm, and be respectful of the patient's and family's wishes in the process—what we term the fundamental arc between respect for autonomy and beneficence. As health care providers, we need to determine the best interests of our patients and strive to understand and support those interests. In other words, we need to mitigate the risks of telehealth and realize its benefits in order to prevent harm and do good.

Understanding risks and benefits, of course, is a standard part of the informed consent process, but interestingly, Baker and Bufka have noted that most states do not require informed consent specific to telehealth.[27] That said, we expect this to change rapidly in the United States as access to and use of electronic devices integrates even further into

our social fabric, and state legislators grapple with applications of HIPAA and the implications of the use of mobile devices in health care monitoring, education, and treatment. Although it is important to ethical practice for practitioners to understand current consent requirements set by their state board, we clearly believe it is a best practice for providers to seek consent for electronically mediated health care services from their patients and clients regardless of the regulatory environment.

As we defined in the first edition of this text, informed consent requires the patient or surrogate to communicate an uncoerced, reliable health care decision after comprehending and weighing the potential risks, benefits, treatment alternatives, and outcomes. Although it may seem obvious, the health care provider must first know who is giving consent. When someone is face-to-face, this identification is relatively straightforward. However, if consent is solicited remotely, the identity of the user is not necessarily apparent. Potential risk of misidentification obviously decreases when initiating telehealth services with a patient for whom the provider has an established relationship. If an initial in-person assessment is not possible, verification of new patients can be facilitated by use of video or audiotaping. One might also consider having individuals interested in services send a photo, tape, or brief but unique personal background statement along with more standard identifying information (e.g., date of birth) prior to setup of remote service delivery to aid in initial identity confirmation. In its Core Operational Guidelines for Telehealth Services Involving Provider–Patient Interactions, the American Telemedicine Association[28] recommends that patients provide comprehensive identifying information (e.g., full name, date of birth, email, etc.) including a government-issued ID.

There has also been some discussion in the literature surrounding when it is appropriate to use telehealth services and who is appropriate for telehealth services with special consideration given to individuals with severe psychiatric disorders. The APA[29] has advised providers to consider conducting an initial in-person meeting to discuss the unique benefits and risks of telehealth, taking into account cultural and other factors prior to initiating services. Kuemmel and Luxton[30] discussed this issue at the annual rehabilitation psychology conference and recommended the use of an initial in-person assessment when feasible. Their rationale was that it could offer insights into the client that would be more challenging to acquire via telepsychology. They point out that an initial in-person assessment eliminates concerns regarding selection of assessment tools that might be less reliable or valid in an electronic delivery platform. Being face-to-face would also allow for immediate crisis evaluation and response in patients presenting with significant psychological distress who are not yet well known to the provider. Their stated preference was to use telepsychology with clients with reduced suicidal risk and good social support. That said, there are examples in the literature supporting telehealth services for those under significant distress. Gros, Veronee, Strachan, Ruggiero, and Acierno[31] shared a case example of a military veteran living in a rural community who presented with suicidal ideation. They indicated telehealth actually facilitated patient safety because the provider had the opportunity to stay directly connected to monitor the patient's status while plans were implemented for the individual's safe transportation to an inpatient unit. In general, the evidence is mounting that telehealth can be used with a variety of different patients with equal or better clinical outcomes and patient satisfaction.[32,33]

Depending upon the types of information the health care professional will need to assess, telehealth still may or may not be the most appropriate format. Luxton, Pruitt, and Osenbach[34] provide an excellent summary on the potential limits of telehealth assessment, pointing out, for example, that sensory data and physical and other nonverbal cues health care providers commonly rely on can be compromised or unavailable. They further remind us that not all assessment tools are well suited for remote administration, have not been normed this way, and may be responded to differently by different cultural groups. Depending upon the data being gathered, health care providers need to thoroughly consider the advantages and disadvantages of remote assessment and the potential options for eliminating the disadvantages through proper setup and management of the provider's and patient's environment. Proper camera positioning, use of magnification equipment, and use of presenters are a few examples of modifications that can enhance results. Setting adjustments may be particularly relevant when working with people with disabilities with whom consideration must be given to the role of caregivers during assessment as well as tool/equipment adjustment needs affected by functional limitations (e.g., reduced mobility and coordination to manipulate electronic materials, visual and hearing impairments affected by equipment quality, dysphagia, dysarthria for which understanding can be complicated by sound quality, cognitive impairments, etc.). Fortunately, equipment and setting modifications are becoming increasingly sophisticated in an attempt to address these types of assessment issues.

Once the provider is reasonably sure of the client's identity and the general appropriateness of telehealth based on any available referral information, there will be a number of unique considerations in acquiring informed consent prior to initiation of telehealth services. Patients will vary widely in their sophistication and comfort in using electronic health services, and it behooves the health care provider to thoroughly describe the types of services to be provided, discuss the pros and cons of using telehealth services in attempting to reach specific health outcomes, and to understand and address any patient reservations in order for the patient to provide informed consent. Unique areas to be included in the informed consent process include, but are not limited to, the following:

- Confidentiality, particularly in the remote location
- Privacy and security of the electronic milieu
- Storage of and access to material

- Management of technical difficulties
- Emergency plans
- Involvement of third parties
- Management of boundaries
- Fee structures and costs to deliver care

Given the proliferation of and access to the technologies serving as telehealth platforms, one important focus of telehealth informed consent needs to be the patient's understanding of the limits to privacy protection. Risks of breaches in security and confidentiality are not uniquely associated with telehealth, but with telehealth comes increased risk. Conducting any type of therapy remotely, for example, creates the need for sensitivity to the environment in which the patient chooses to receive that therapy. Do you know where your patient is and how secure his or her equipment is? Do you know how confidential the environment will be during the time of service provision? Providers should not assume the patient is going to independently create a secure, confidential environment, and the limits of the environment necessitate discussion regarding both privacy and confidentiality. These considerations are also a two-way street. A patient, especially one growing up with electronic media, may have broader tolerance than the provider for unsecured information sharing or lack of confidential surroundings. The provider needs to be clear on how insecure is too insecure for the health topics being addressed based on any applicable laws, regulations, and ethical expectations.

As suggested in *the Telerehabilitation Guidelines*,[35] providers must be aware of privacy and confidentiality requirements at both the originating and remote site. Therefore, providers must clearly understand both theirs and their clients' settings. Luxton, Pruitt, and Osenbach[30] suggest that distractions in the home environment can affect the assessment process and need to be minimized. Agreement on the types of settings in which services will be delivered should be solicited during the consenting process. Family members can play an important role in facilitating this for persons with traumatic brain injury with residual attentional issues. Given the provider will lack control over the remote environment, engaging family in creating and maintaining confidential, nonchaotic space can help optimize engagement of persons with severe attentional or behavioral issues. The provider, in particular, also needs to consider the costs of encryption and secure servers or other systems for transmitting and housing data as well as discuss the risks inherent in computer-based usage, such as potential viruses and hackers attempting to gain private personal information. Does the necessary investment to create a more secure environment make sense in the context of the services to be rendered? Striving for the most secure environment rather than a minimally acceptable level should be the standard of practice, taking into account professional obligations (e.g., conduct codes and laws), reasonable costs, and patient preferences. Fortunately, there is an ever-growing list of tools that make security more feasible with continuing advancements in technology.

Despite the best setups, technical glitches are going to occur, ranging from phone lines being down and difficulty logging into computer systems to technical failures causing service interruption and possible therapeutic disruption with negative effects. As part of the consenting process, it is important for the patient to know these types of electronic malfunctions are likely to occur and for the provider to gauge the patient's comfort with these types of episodes. Equally importantly, the provider should include what plan will be implemented if these, in fact, do occur. In order to have thorough consent as well as practice ethically, providers must lay out backup plans for technical failures. For example, will the session be terminated if it is more than halfway through when a disruption occurs if the patient is not experiencing signs of distress; will the patient be billed for sessions that are interrupted and terminated; will alternative access be attempted and under what circumstances? These are the types of questions patients must understand the answers to when making a decision to engage in services being delivered electronically. The consent process also provides the opportunity to discuss options for protecting patient appointment time. For example, if there is only one computer or phone, the option of setting up an alternative line should be raised with the patient such that the benefits and costs can be weighed.

Technical failures are not the only areas requiring backup plans. Preventing harm and keeping the patient safe during service delivery are paramount, and consistent with the principle of beneficence, the provider must present plans for dealing with the patient's unexpected health needs. Similar to onsite service delivery, emergencies for medical or psychiatric reasons can occur during the service appointment, and response teams need to be in place to deal with each. Unlike hospital and clinic settings that have built in safeguards, telehealth systems require the provider to establish a concrete safety plan that can be implemented remotely. The provider needs to know the phone number to the closest hospital or clinic providing emergency care for both physical and psychiatric needs. Providers and patients should also agree on backup to the primary mode of communication such that there is a clearly defined alternative to acquire help, if needed. Thus, the health care provider needs to ensure someone else is accessible and geographically close during appointments. Caregivers of individuals with TBI, strokes, or other disabilities are often key contributors here. Community members, such as pastors, are also possible resources. Patients and/or families clearly need to participate in the development of these plans as part of the informed consent discussion to ensure the plans are sustainable for the predicted duration of services.

In addition to discussing emergency plans that exceed typical boundaries, the informed consent process must also include a discussion of how to manage more typical practice boundaries. As one might imagine, without clear limits regarding communication, communication could become increasingly social and intrusive, negatively impacting the therapeutic relationship. Clear understanding from the outset

sets the stage for a productive patient–provider relationship across time. In setting appropriate boundary expectations, it is recommended providers clarify how several items will be managed, such as the following:

- Setting up appointments
- Cancellations and rescheduling
- Respect for time boundaries related to scheduled sessions
- How to contact the provider outside of any scheduled appointments and under what circumstances
- The provider's commitment to appropriate information sharing and prevention of inappropriate boundary crossings
- Termination of services

The flexibility of telehealth may create the illusion that time and setting do not matter. The instantaneous nature of feedback in social media reinforces behavior that is more relaxed. Therefore, the provider needs to distinguish social interaction from the development of a professional relationship. For example, given the pervasiveness of mobile devices that could be used to deliver reinforcing therapeutic messaging at specified times, misunderstanding could arise regarding the acceptability or frequency of more personal contact between sessions.

Interestingly, Drum and Littleton,[36] who provide a comprehensive discussion of boundaries, suggest that providers may inadvertently reinforce casual interactions when they conduct sessions in informal settings. It behooves the provider to set clear, reasonable boundaries. Telehealth videoconferencing also introduces the possibility of unintentional self-disclosure based on visible objects, items, or people moving through the camera field. The risk of this type of disclosure damaging the relationship may be minimal, but it is up to both the provider and patient to set up a comfortable environment. Discussing these issues at the outset can help build the trust necessary to establish a positive therapeutic relationship.

The ultimate goal of this relationship, of course, is to maximize functional clinical outcome based on the concrete manifestation of beneficent actions while respecting patient autonomy. The promise of telehealth partially lies in the fact that patients who would not otherwise access health care can now do so, creating an opportunity for more equitable distribution of health care services (upholding the principle of justice). People in rural communities without health care specialists, individuals with mobility impairments limiting amount and/or frequency of travel, individuals requiring functional assistance with limited access to caregivers, military personnel serving in remote locations, individuals without transportation, and individuals who require maximal structure and consistency can all realize the potential benefits telehealth offers. By mitigating the risks previously discussed in the context of the informed consent, access to telehealth can save the patient time and money and result in improved clinical outcomes. In one case study, for example, families of children with TBI requiring CT scans saved travel time and money when a hospital in Montana launched a follow-up video assessment of the children.[37]

The provider can also realize parallel benefits, such as flexible scheduling and patient monitoring resulting in successful interventions. However, reaching beyond in-person service delivery does create additional ethical and risk management sensitivities for the provider. Two highlighted repeatedly in the literature that we briefly comment on here are practice jurisdiction and practice competence.[22,28,38] Because telehealth separates the provider from the client, very real risks emerge regarding licensure requirements. Practitioners obviously should be licensed to practice in their home state, but are they required to have a license to practice in the client's state if different than their own? Currently, very few professions have interstate agreements around telehealth although some states allow time-limited consultation and/or treatment more generally. This means that providers would require a license in each state in which their patients reside. Recall, however, that state laws and regulations vary, and it is important for providers to understand what laws, if any, exist in each state in question. The provider needs to understand how the states involved (both states of residence for the provider and patient) define and govern telehealth services. This obviously can quickly become a significant barrier to practice as noted by the American Speech-Language-Hearing Association in its State of Telepractice in 2014 survey summary.[39]

Finally, ethical practice mandates competent practice. Some researchers have reported that a significant percentage of providers feel inadequately prepared in telehealth.[40] Brooks, Turvey, and Augusterfer[41] reference a variety of different types of training programs that have arisen in the past decade, such as continuing education seminars, webinars, and certificate programs. We anticipate that providers' perceptions regarding training will become increasingly positive as they gain exposure to telehealth practices and appropriate uses and modalities and as relevant research publications continue to document positive patient outcomes.

CONCLUSIONS

The appealing aspect of this discussion of ethics in selected dimensions of health care is that the reader can appreciate specific facets of the health care system that individuals can directly influence through personal action as opposed to those under the influence of sociopolitical forces. We often feel most comfortable when we can directly affect life situations, exercising autonomy, acting with beneficence, and protecting against maleficent acts. However, when we must confront distributive justice, we realize that policy makers external to our spheres of direct influence have the advantage but also the social responsibility to act accordingly.

The topic of patient rights and responsibilities during recovery from traumatic brain injury can be brought under the direct influence of survivors, family members, health care providers, and community resource professionals. With intimate understanding of the effects of such injury upon health, cognition, emotional function, physical performance, social relationships, community integration and vocational pursuits, rehabilitation offers survivors and family members practical tools to support and accommodate functional recovery—with attaining a functional measure of individual autonomy as a realistic treatment goal.

On the other hand, health care reform falls in the ethical bailiwick of policy makers and legislators, who it is hoped operate under the principle of distributive justice—seeking equal and affordable/attainable access for all citizens and removing barriers to system access and service availability. The voters, adequately informed about issues central to health care reform, can evaluate the performance of their legislators as their actions directly impact everyday living and then vote accordingly. Unfortunately, a barrier to an adequate level of understanding of such complex social issues as health care is the partisan polemic that pervades social media. It appears that messages containing emotional "hooks," often shading the facts in an affectively charged manner, tend to influence the populace more than the legislative proposals themselves—typically shrouded in cloaks of formal legal language that is difficult to decipher. However, another legislative system puts significant power in the hands of the informed voter.

Another avenue of action to pursue in matters of policy and law is public advocacy. This can be accomplished on an individual basis by offering testimony regarding health care access and service availability for survivors of traumatic brain injury and families to state and federal legislators and policy makers in hopes of crafting legislation. This advocacy process can be further strengthened in alliance with national organizations, such as the BIAA.

Telehealth, as a health care service delivery phenomenon, is just beginning to have an influence on health service delivery. It presents us with a mixture of impressive technological development and application possibilities whose operative horizons are not fully defined. Yet, the common denominator for the relevance of this technology remains the health care consumer.

In that arena, ethics applied to telehealth finds its footing in the principles of autonomy, beneficence and nonmaleficence when applied to telehealth. Both the health service consumer and provider can evaluate their decisions and actions against the ethical criteria subsumed under those principles: preserving self-determination, doing good acts, and avoiding harm. To the extent that a particular telehealth modality adheres to ethical practice standards, it clears a significant hurdle toward effective utilization. With the forethought afforded us during the current development phase of telehealth applications, we can advocate for building patient protections into varied telehealth methodologies before wholesale adoption and implementation occur with the forethought afforded us during the current development phase of telehealth applications.

The take-home message is that ethical principles and standards are accessible, practical, relevant, and are part and parcel of our daily activities in health care and in everyday living. They help us evaluate our life situations and those of others in a fair and equitable manner, preserving the dignity of the human condition. Consciously adhering to those time-tested tenets allows us to function optimally when challenged and to find comfort and safety in the mundane.

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