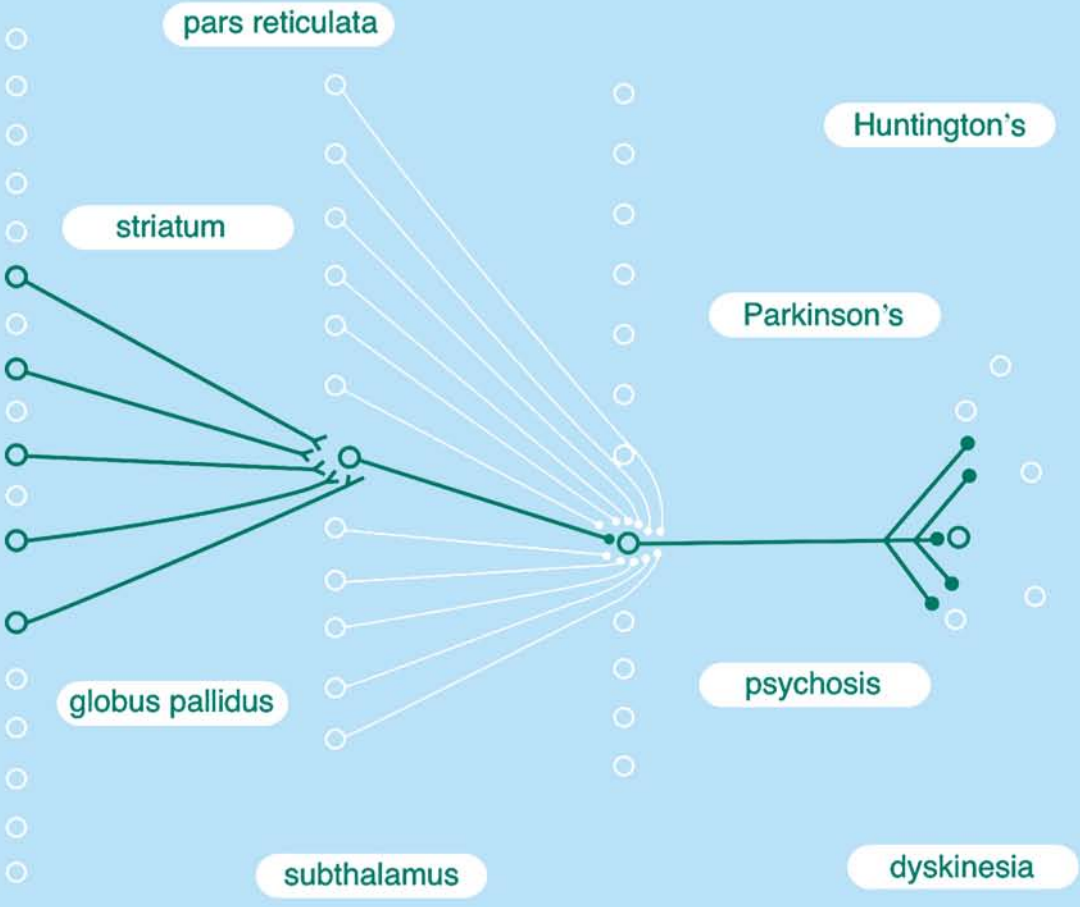
CABR Conceptual Advances in Brain Research

A Theory of the Basal Ganglia and Their Disorders

Robert Miller



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A Theory of the Basal Ganglia and Their Disorders

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A Theory of the Basal Ganglia and Their Disorders
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Series Preface

The workings of the brain, including the human brain, are a source of endless fascination. In the last generation, experimental approaches to brain research have expanded massively, partly as a result of the development of powerful new techniques. However, the development of concepts that integrate and make sense of the wealth of available empirical data has lagged far behind the experimental investigation of the brain. The series of books entitled *Conceptual Advances in Brain Research* (*CABR*) is intended to provide a forum in which new and interesting conceptual advances can be presented to a wide readership in a coherent and lucid way.

The series will encompass all aspects of the sciences of brain and behavior, including anatomy, physiology, biochemistry, and pharmacology, together with psychological approaches to defining the function of the intact brain. In particular, the series will emphasize modern attempts to forge links between the biological and the psychological levels of describing brain function. It will explore new cybernetic interpretations of the structure of nervous tissue; and it will consider the dynamics of brain activity, integrated across wide areas of the brain and involving vast numbers of nerve cells. These are all subjects that are expanding rapidly at present. Subjects relating to the human nervous system as well as clinical topics related to neurological or psychiatric illnesses will also make important contributions to the series.

These volumes will be aimed at a wide readership within the neurosciences. However, brain research impinges on many other areas of knowledge. Therefore, some volumes may appeal to a readership, extending beyond the neurosciences. Books suitable for the series are monographs, edited multiauthor collections, or books derived from conferences, provided they have a clear underlying conceptual theme. To make these books widely accessible within the neurosciences and beyond, the style will emphasize broad scholarship comprehensible by readers in many fields, rather than descriptions in which technical detail of a particular speciality is dominant.

The next decades promise to provide major new revelations about brain function, with far-reaching impact on the way we view ourselves. These great breakthroughs will require a broad interchange of ideas across many fields. We hope that the *CABR* series plays a significant part in the exploration of this important frontier of knowledge.

Preface

The basal ganglion, to adapt a phrase of Churchill's, is "a riddle wrapped in a mystery inside an enigma." These structures are a minefield for theoreticians of brain function, for several reasons. First, there are a number of different nuclear structures within the basal ganglia, each with different roles, but all collaborating in the overall dynamics of the basal ganglia. In this respect, the basal ganglia are more complicated than the much larger cerebral cortex, which, despite its formidable complexity, has a degree of overall uniformity. Second, most of the neurons in most of these component nuclei are inhibitory. As a result, in the interaction between the different nuclei, there are endless possibilities for reversals of the mathematical sign of influence, and the number of such reversals is a matter of debate. Consequently, there are many alternative suggestions of how the various nuclei might actually operate together. Third, the fundamentals of anatomy and physiology of the basal ganglia are best known to basic scientists. However, some of the key facts for understanding them are clinical facts best known to a different group of researchers, those with everyday experience of assessing and treating disorders of the basal ganglia in human patients. In addition, some of those essential clinical facts are in the field of neurology and some in the field of psychiatry. In the nineteenth century, these two branches of medicine were part of a unified discipline concerned with "nervous and mental disorders." Since then, in many countries, the two disciplines have diverged. While medical traditions in some countries have preserved the two specialties as part of a unified discipline, in many parts of the world, psychiatry and neurology have, for many years, developed along different lines, and have built up differing traditions, with inevitable barriers to communication between the two. In the present work, I (with no qualifications in either of these medical specialties, but a background in the overall theory of the mammalian forebrain) attempt to resolve the riddle of the basal ganglia, and to place the essential clinical facts from both neurology and psychiatry within the framework formulated for normal operations of the basal ganglia.

This monograph has two parts, the first dealing with the basic framework in which normal functions of the basal ganglia can be understood and the second focusing on major disorders of the basal ganglia. In fact, the division between normal and abnormal operation of the basal ganglia is not followed through in a strict fashion: Some clinical facts (e.g., about Huntington's disease) are important in developing ideas about the basic framework; and some basic facts about the normal organization of the basal ganglia (e.g., the role of the striatal cholinergic neurons) are not essential in formulating the basic framework, but are more relevant in the context of disorders of basal ganglia. Moreover, the reader should not expect that all disorders arising in the basal ganglia are analyzed in Part II. The aim of this part is to explain, as far as possible, symptoms and related clinical facts in terms of underlying pathology and pathophysiology (i.e., cell loss or changes in firing frequency in cell groups). With this as the aim, disorders of the basal ganglia are included only when there are already clear ideas about the underlying neuropathology or pathophysiology.

Sometimes these ideas are already well established, while at other times the argument is based on plausible proposals, which are still under evaluation. Theories stand or fall by what they predict. Therefore, in the synopses of both Parts I and II, specific mention is made of the predictions following from the theory presented here, as well as significant points that are not yet dealt with by the theory.

Chapter 9 discusses psychosis. There is one aspect of this chapter, which I feel I should explain here to avoid possible misunderstandings. My particular interest in this topic goes back 40 years, when, as a young man, I experienced two florid psychotic breakdowns. I have very clear memories of this time, especially of the second of these episodes. The story of this period of my life was put in writing in the 1970s, and the account was eventually published quite recently. As someone who had already embarked on neuroscience research, these episodes provided me with strong motivation to understand, and a rich source of first-hand experience upon which to draw. This led, in the mid-1970s, to my first attempts at scientific formulation of the abnormalities of information processing in psychosis, and, by 1981, to ideas about dopamine-mediated synaptic plasticity in the striatum. In a broader perspective, these experiences have opened up the whole field of the dynamic operations of the basal ganglia (dealt with here), as well as wider issues about the nature of the disorder called schizophrenia. Those experiences were the real origin of the present work. A number of my previous papers have wrestled with aspects of the functions of the basal ganglia, but have never had a sense of completion. The present book might just have achieved this.

Acknowledgments

I would like to thank a number of organizations and individuals for support in the years when this work was in gestation. The University of Otago in New Zealand, especially the Department of Anatomy and Structural Biology, and the staff of the medical library there, are thanked for their support, partly in the years when I was employed at Otago University, and especially since 2000, when, having resigned my position, I retained very useful links with the university, and was given the status of Honorary Fellow. I thank the Deutsche Forschungsgemeinschaft for financial support, which allowed me to spend a year (2002–2003) at the Zentral Institut für seelishe Gesundheit, in Mannheim, when Part I of this work was assembled. I thank the Jewish Community Endowment Fund, for support in the year 2004–2005, spent at McGill University, Montreal, when Part II was completed. Some of the ideas presented in Part II arose in part from a visit, financed by the pharmaceutical company Eli Lilly, to its headquarters at Indianapolis, and later at the Schizophrenia Congress in Santa Fe. My thanks to the Schizophrenia Fellowship of New Zealand for its steadfast support of all my research endeavors.

Among the many individuals whose work has assisted in the synthesis in this monograph are several neuroscience researchers at the University of Otago—Jeff Wickens, Dorothy Oorschot, John Reynolds, Brian Hyland, Jason Kerr, and the late Mark Tunstall—all of whom have contributed important empirical facts incorporated mainly into Part I.

In Canada, I would like to thank Guy Chouinard, who, as a collaborator for over 15 years, has given me steady support, as well as enlightenment on many clinical matters. This was crucial in the development of both the psychiatric and neurological sides of the theory developed in Part II. I also thank Rick Beninger for a long-standing collaboration on the basic scientific aspects of the psychological function of dopamine. I thank Gordon Arbuthnott for his encouragement, after reading a draft of this book. I thank Ross Marshall-Seeley for his help in computing and formatting of the manuscript, and Robbie McPhee for all artwork presented here.

In Germany, I thank Neils Birbaumer, Almut Schüz, and Valentino Braitenberg for their support and encouragement. Valentino has said to me on several occasions that the field of inquiry where the cybernetic interpretation of brain function, which he has pioneered, should find its most exciting challenges and most exacting testing ground is in clinical areas, in understanding neurological, and especially, psychiatric disorders. I hope he will find this work to be a worthy start in realizing this vision.

Robert Miller
Dunedin

Author

Robert Miller was born and educated in Great Britain, with degrees from Oxford and Glasgow. In 1977, he emigrated to New Zealand, where, until 1999, he was on the teaching staff of Otago University (Department of Anatomy and Structural Biology). During these years he developed a distinctive strategy of library-based theoretical work into brain function, and its relevance for understanding major mental disorders. He has published many papers, and several scientific monographs on aspects of the function of the mammalian forebrain, the present work being the fourth. In July 1999 he resigned his university position to work as a freelance researcher, but retains links with his former department. In January 2007, he was awarded the New Zealand Order of Merit for services to schizophrenia research.

Part I

The Framework for Normal Basal Ganglionic Function

1 Introduction: Background to the Dynamics of the Basal Ganglia

1.1 THE CORTICO-THALAMO-HIPPOCAMPAL EXCITATORY NETWORK: SUBSTRATE FOR CELL ASSEMBLIES AND ASSOCIATIVE OPERATIONS

The mammalian forebrain consists of various macrostructures of which the cerebral cortex is the largest. This laminated sheet of gray matter comprises both the neocortex and other laminated components, including notably, the hippocampal formation. In addition there are nonlaminated structures in the forebrain, including the thalamus, and a variety of other entities (striatum, globus pallidus, subthalamus), which, together with the substantia nigra in the midbrain make up the complex known as the basal ganglia.

The cerebral neocortex is a vastly complex neural network receiving important inputs from all major sensory systems (visual, auditory, somesthetic), and with a prodigious number of connections, both local and distant, between its several areas. Its principal neurons are pyramidal cells, which have excitatory influences upon each other. Many of the synaptic connections by which the pyramidal cells influence each other—perhaps all—are subject to synaptic modification according to the rule proposed over 50 years ago by Donald Hebb (1949; for recent demonstrations see Hirsch and Crepel, 1990; Baranyi et al., 1991; Kirkwood and Bear, 1994). The cerebral cortex is generally conceived as a cybernetic machine concerned with (first) learning to detect and (later) recognizing statistically significant associations between activity in the many input signals arriving in each cortical locus (Miller, 1981; Braitenberg and Schüz, 1998). As a result, the most commonly adopted theory of cortical function is based on the "cell assembly" concept, another of Hebb's proposals (Hebb, 1949; Braitenberg, 1978; Sakurai, 1996; Miller, 2002). According to Hebb, a cell assembly is formed by the processes of synaptic modification, which he postulated. These two ideas together constituted the backbone of the first overall neuropsychological theory of the cerebral cortex. When formed, a cell assembly is a collection of cortical cells with mutual excitatory connections, making it functionally more strongly connected within itself than it is with other surrounding neurons. As a result, when some of the members of a cell assembly are activated above a critical level, the assembly as a whole becomes active ("ignition": Braitenberg, 1978). Such activity in each cell

assembly is held to represent a "concept" or "percept"—each of which is defined by the regular conjunctions of signals relayed to the different parts of the corresponding assembly. An important assumption implicitly made about the cortex, which is also implicit in cell assembly theory, is that the informational inputs (at least to the neocortex) are analyzed in an "objective" way, purely according to the statistics of association of signals arriving at each pyramidal cell, and unbiased by general considerations of the motivational significance of these signals.

Electrophysiological research in the last 20 years has provided evidence that individual impulses in the impulse trains from each pyramidal cell may sometimes be quite precisely timed. For instance, impulse trains from single neurons may show above-chance recurrences of exactly timed sequences of several impulses (Dayhoff and Gerstein, 1983; Villa and Fuster, 1992). Moreover, when impulse trains from different neurons recorded at the same time are compared, there may be above-chance repetitions of exactly timed impulse patterns shared between the different trains (Abeles et al., 1993; Villa, 2000). Furthermore, there is increasing evidence that such exact timing of impulses correlates with behavior (Villa, 2000) or with sensory analysis (McClurkin and Optican, 1996; Victor and Purpura, 1996), and there is increasing acceptance that exactly timed patterns of impulses may be of general significance in the information processing accomplished by the cortical network. As a result, reformulations and reinterpretations of the original cell assembly concept have been proposed (e.g., the "synfire chain" concept [Abeles, 1982a, 1991]) to take account of the precise temporal structure within impulse trains, revealed experimentally.

A related aspect of cortical neuronal physiology in these formulations depends on the general assumption that summation of the effects of several coactive afferents is needed to fire a neuron. From the fact that there can be rather exact timing of impulses, it then follows that the integration time of single neurons should be quite narrow, spanning a period of the same order as the small temporal "jitter" seen in the timing of impulses. The magnitude of this "jitter" in temporal patterns in multineuron trains is hard to determine accurately, but is probably sometimes as small as 5 ms (McClurkin and Optican, 1996; Victor and Purpura, 1996). This fits with data from *in vitro* preparations, showing that under some conditions, single pyramidal cells can generate impulses accurately time-locked to peaks in injected current pulse regimes, even when the latter fluctuate at frequencies of several hundred cycles per second (cycle time of just a few milliseconds) (Carandini et al., 1996; Nowak et al., 1997).

From the perspective of the present book, it is important to point out that exact timing of impulses also requires that excitatory (but not inhibitory) processes determine the timing of impulses. This follows from the fact that inhibitory postsynaptic potentials (henceforth IPSPs) can specify only the time when impulses are absent, not when they are present. Thus, we have another indication that the essentials of cortical neuronal dynamics rely on excitatory interactions, with inhibitory interactions having a subsidiary role. The temporal precision of impulse firing is then determined by the temporal latitude permitted, given that coactive inputs to a pyramidal neuron must coincide within the time-span of a single excitatory postsynaptic potential (henceforth EPSP). This period (the "integration time" for the pyramidal cell) is of the order of 10 ms, though it may vary in different circumstances.

If this model of cortical dynamics is correct, there are other closely related implications: First, it is known that long cortico-cortical axons often have conduction times of several (even many) tens of milliseconds, far longer than the integration time of single pyramidal cells (Miller, 1994; Swadlow, 2000). Given that single impulses in cortical pyramidal cells may be quite accurately timed, and that they reflect the activity circulating within the cortical network, delays due to axonal conduction must be important in determining the timing of neuronal firing. To put this another way, pyramidal cells "select" sets of afferent inputs, such that the EPSPs these afferents produce in each pyramidal cell occur together within the same integration interval despite the fact that the presynaptic cell bodies giving rise to these EPSPs have been activated at times dispersed much further than a single integration interval. In accounting for the accuracy of timing of impulses, pyramidal cells have thus been conceived as "coincidence detectors" (Abeles, 1982b). A key question then is: "How many afferent synaptic activations must coincide within a single neuronal integration time to bring the cell to firing threshold?" The answer to this question is a matter of debate. However, there is evidence that in the waking state the membrane potential of pyramidal cells exhibits bistability: There is a "down state" in the region of −70 mV, but these cells can sometimes also hold membrane potentials relatively stable within 5 mV of firing threshold (Metherate and Ashe, 1993; Cowan and Wilson, 1994; Stern et al., 1997; Timofeev et al., 2001). In the latter case, it is expected that a relatively small number of unitary EPSPs need to coincide to fire the cell.

In recent years, attention has been drawn to the fact that neurons of the thalamus both send to and receive from the neocortex a large number of connections. The connections in both directions between thalamus and cortex are excitatory, like the cortico-cortical connections themselves. The thalamus may thus be involved in two-way excitatory interplay with the neocortex. Several papers have shown that the exact timing of spike firing seen in multineuron recording of spike trains in the cortex also applies to the thalamus (Villa, 2000) and can again be related to details of sensory processing (Nicolelis and Chapin, 1994). However, thalamic principal neurons have no local axon collaterals by which they can excite one another and which could play a part in the temporal coordination of their impulse firing. Since cortical inactivation can reduce the occurrence of temporal coordination of spikes in thalamic cells (Villa, 2000; Ghazanfar and Nicolelis, 2000), such coordination is likely to be generated by interplay with the cortex rather than by local interactions. It has therefore been suggested that the principal neurons of the thalamus are closely involved in cell assembly formation, especially in coordinating the activity of cell assemblies, which are spread across wide areas of the neocortex (Sherman and Guillery, 1996; Miller, 1996). According to such a concept one can regard the component neurons of cell assemblies located in the thalamus not so much as "relay neurons" to the thalamus, but as "points of control," at which cortico-thalamic cells assemblies could be switched on or switched off (Miller, 1996). The "ascending" excitatory input to thalamic principal cells from sensory and other pathways can then be easily interpreted as control lines capable of switching *on* a cell assembly. The alternative possibility that there also exist inhibitory control lines devoted to switching *off* a cell assembly is one of the central foci of Part I of this book, referring especially to the influence of the basal ganglia on the cortico-thalamic network.

It has also been pointed out (Miller, 1991) that the neocortex, being a network in which signals are anatomically capable of immense divergence and convergence, inherently has a considerable degree of uncertainty or ambiguity in the information which can be encoded singly or multiply by its neurons, when signals are transmitted across more than a single synapse. In anatomical terms there are many reentrant circuits between neocortex and the hippocampal formation, which, like those of neocortex and thalamus, are excitatory. A specific proposal has been made that, from these anatomically defined reentrant circuits, functionally effective loops can form during learning, which serve to "disambiguate" the neocortical network (Miller, 1989, 1991). Thus, specific "subnetworks" come to be selected to deal with the information processing needed in each context, which the environment presents to the organism. As a result, the various local or distributed cell assemblies, which are brought into activity in each context can be coordinated in a unique pattern of cortico-hippocampal resonance. Consequently, cortical regions other than the neocortex, notably the hippocampus have become implicated in cell assembly formation.

Overall, one can conceive that three major macrostructures of the forebrain—neocortex, thalamus, and hippocampus—are parts of a vast network of connections, essentially excitatory in nature (although all three structures have local inhibitory processes), which via the cell assembly structures it supports, performs, or elaborates the basic associative function of the forebrain (Figure 1.1). Henceforth, this will be referred to as the "CTH network". The computation in this network is essentially local, because the essential synaptic interactions and processes of synaptic modification are local functions of pyramidal neurons (or thalamic principal cells) and their afferent synaptic boutons. Admittedly, from the massed computations of the CTH network, an overall "consensus" view may arise about what is "salient." Moreover,

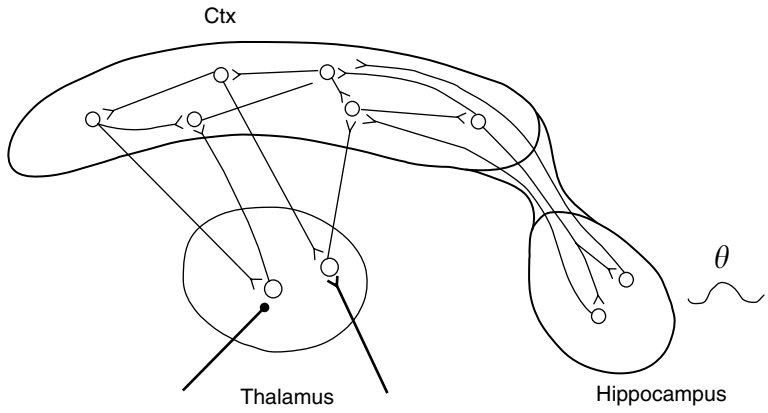


FIGURE 1.1 Schematic diagram of the cortico-thalamo-hippocampal (CTH) network. Assemblies are organized primarily in the cerebral neocortex (Ctx), but have member neurons throughout the thalamus, and are also entrained in rhythmic interplay at the theta (θ) frequency with the hippocampus. Thalamic member neurons can be seen as control points, so that assemblies can be switched on via excitatory inputs, such as ascending sensory pathways (bold connection, *right*: ——≺) afferent to the thalamus, and can be switched off via inhibitory ones (projections from the basal ganglia: bold connection, *left*: ——●).

signals about the behavior of the whole organism may be fed into the CTH network from other parts of the brain. However, the key point here is that the synaptic processes in the CTH network appear not to be determined in a critical way by the needs of the whole organism and the motivational significance of its emitted behavior, but locally, according to the statistics of activity relayed to each neuron along its various afferent lines.

1.2 DEFINITION OF EXECUTIVE FUNCTIONS

Mammalian behavior is not (and could not be) controlled solely by a machine devoted exclusively to associative processes. Certainly, these are likely to be one of the fundamental ways of analyzing incoming information, but additional processes are required to determine behavioral output. In particular, it is required that clear decisions are made about the behavioral strategies to be followed in any of the situations presented by the external environment. These "executive decisions" refer to the requirements of the whole organism. The word "requirements" refers mainly to the consequences of behavior in relation to the motivational needs of the whole organism. Knowledge of such relations is gained as the organism experiments with the environment, so that an experienced animal or human knows the strategies of behavior, which will fulfill its motivational needs in each situation. In analogous fashion, even when there is no overt behavior, executive decisions are made about the current focus of selective attention. Thus (just as for control of overt behavior), clear decisions need to be made between alternative foci of attention, again bearing in mind the (temporary) goals of the organism as a whole. It is thus no coincidence that the term "central executive" is used in psychological theory to designate the function envisaged to take decisions about the apportionment of attentional resources in the conscious animal, as it interacts with its environment (Baddeley, 1986).

However, as mentioned above, cortical processing is dictated essentially by local cybernetic operations, processing at each locus being ignorant of global goals. Admittedly, the CTH network may be subject to global controls governing the level of consciousness, but, at least in the neocortex, there appear to be no explicit signals directly conveying information about motivational relevance. Nevertheless, signals about the motivational significance of possible behavior, and of the possible targets of attentional focus need to be somehow introduced into the operations of the forebrain including the cortex. These signals would be of a category quite separate from the sensory signals delivered to the cerebral neocortex (supposedly analyzed in an "objective" way, unbiased by considerations of their motivational significance).

As far as cell assembly function goes, the essentially excitatory CTH network summarized above is ideal for associative processes. However, the function of "decision making" about behavioral or attentional strategies is exactly the opposite of association. It might be envisaged that each strategy of behavior or focus of attention is mediated by its own cell assembly. However, when each such cell assembly is called into action by an executive decision, it alone needs to be called forth, uninfluenced by any other assembly. For instance, if the current environmental situation is reminiscent of more than one past situation, an associative network might produce links between the corresponding assemblies mediating behavior, and

merging or "uneasy compromise" between quite different strategies of behavior might be expected to occur. However, this would prevent any single strategy from running its course smoothly to the point of goal fulfillment. Likewise, close attention to one focus of attention necessarily largely precludes that to another. Thus, executive decisions need to be sharp categorical ones, excluding activity in all cortical neurons, which are not part of the strategy that has been decided upon. To say "if strategy A is adopted, then strategies B, C, D (etc) must be suppressed" implies important *inhibitory interactions* rather than solely excitatory ones. In short, to make executive decisions, whether about behavior or about the focus of attention, something is required beyond the essentially excitatory interactions of the CTH network to break the symmetry of that network.

1.3 THE "MOTOR THALAMUS": TARGET OF EXECUTIVE DECISIONS?

Within the CTH network, the region that holds greatest promise as the site at which the symmetry of the excitatory network is broken are certain thalamic nuclei (loosely, the "motor thalamus"). In most thalamic nuclei, the main informational input is conveyed exclusively by excitatory influences. In ultrastructural terms, these excitatory inputs to thalamic principal cells are of two sorts (Steriade et al., 1990). The first of these are recognizable in electron microscope pictures as "small round" terminals, located mainly on distal dendrites, and derived from all regions of the neocortex (Jones and Powell, 1969; Jones, 1985; Steriade et al., 1990). The other variety of excitatory terminals are the "large round" boutons (Jones and Powell, 1969; Jones, 1985) located mainly on proximal dendrites, which are derived either from ascending sensory pathways (e.g., Guillery, 1969) or other ascending pathways (Harding, 1973; Somogyi et al., 1978) or (in some nuclei) directly from the cortex itself (Mathers, 1972; Schwartz et al., 1991; Kuroda et al., 1992). These boutons are less numerous than the small round synapses (Tseng and Royce, 1986; Sawyer et al., 1991; Montero, 1991). However, in a few thalamic nuclei (or in subregions of these nuclei), the proximal dendrites of principal cells receive large terminals identifiable not as excitatory but as inhibitory synapses (Rinvik and Grofova, 1974; Kultas-Ilinsky., 1983; Kultas-Ilinsky and Ilinsky, 1990; Ilinsky and Kultas-Ilinksy, 1997). The ultrastructural features permitting such an identification are well known, including symmetrical contacts between pre- and postsynaptic membranes and oval or pleomorphic vesicles in the presynaptic bouton (see Figure 1.2). Various methods of tracing connections have been used that identify these inhibitory connections as being those of axonal projections originating in the output nuclei of the basal ganglia (Kultas-Ilinsky et al., 1983; Kultas-Ilinsky and Ilinsky, 1990). There are two such nuclei, the substantia nigra pars reticulata (SNR) and a nucleus whose name differs between species, being either the entopeduncular (EP) nucleus in rodents or cats or its equivalent in primate, the internal segment of the globus pallidus (GPi) (see diagram in Figure 2.1). The inhibitory nature of these projections is supported by evidence that they contain the inhibitory transmitter γ-aminobutyric acid (GABA) or its enzymes (Di Chiara et al., 1979; Kilpatrick et al., 1980; McLeod et al., 1980; Sawyer et al., 1991; Kultas-Ilinsky et al., 1997; Ilinsky and Kultas-Ilinsky, 1997). The nuclei in which such

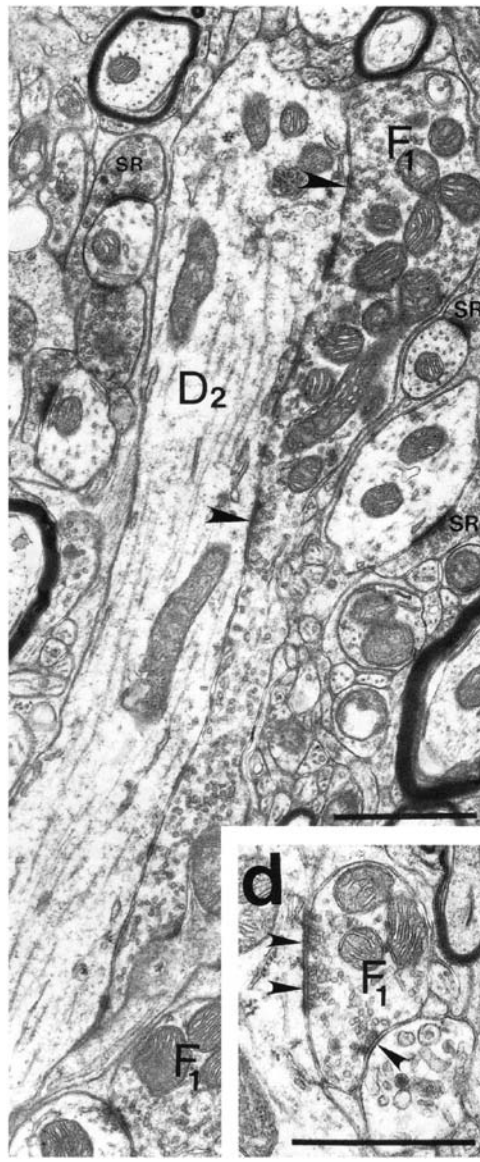


FIGURE 1.2 Inhibitory ("symmetrical") synapses made by pallidal afferents, upon principal neurons of the motor thalamus (nucleus VA of macaque monkey). A large bouton, sectioned longitudinally (F_1), with pleomorphic vesicles forms symmetric synaptic contacts (arrowheads) on a segment of a long dendrite (D_2) of a thalamic principal neuron. d: Detail of synaptic contacts (arrows) between bouton and dendrite. (From Kultas-Ilinsky et al., *J. Comp. Neurol.*, 386, 573–600, 1997. With permission from Wiley.)

synapses (originating from projections in the basal ganglia) are located include VM of rodents and cats (Leonard, 1969; Krettek and Price, 1977; Jiménez-Castellanos and Reinoso-Suárez, 1985; Anderson and De Vito, 1987; Moriizumi et al., 1988), and nuclei VA, VL, and MD in rats, cats, and primates (Carpenter et al., 1976; Hendry et al., 1979; Schell and Strick, 1984; Strick, 1985; Ilinsky et al., 1985; Kemel et al., 1988; Nishimura et al., 1997; Sakai et al., 1998, 2000). These studies mention several other nuclei where the inhibitory connections may also be present but less abundantly.

Many of the thalamic regions receiving from the basal ganglionic output nuclei also receive "large round" excitatory connections from the cerebellar output. Since both cerebellum and basal ganglia are regarded as being involved in motor control, these thalamic regions upon which they project have been referred to as the "motor thalamus." In nucleus VM of the rat thalamus, there is electrophysiological evidence that the inputs of opposite sign from the two sources converge and interact in single neurons (Chevalier and Deniau, 1982; McLeod and James, 1984; Buee et al., 1986). In higher mammals, such convergence is rarely found, and the inhibitory afferents from the basal ganglia target mainly regions or subregions of thalamic nuclei different from those targeted by the excitatory cerebellar afferents (Hendry et al., 1979; Schell and Strick, 1984; Strick 1985; Sakai et al., 2000). There is some recent debate about whether *all* of the thalamic projections from EP and SNR are GABAergic, with some evidence suggesting that a sizable proportion are cholinergic (Kha et al., 2000, 2001). There are however some hints that the latter innervate thalamic nuclei additional to those usually included in the "motor thalamus" (parafascicular nucleus, habenula). Moreover, some of the early electrophysiological studies claimed that the inputs from basal ganglia output nuclei were excitatory. However, the vast majority of electrophysiological, ultrastructural, and cytochemical data accumulated in the last 20 years suggest that the projections from EP/GPi and SNR to the motor thalamus are inhibitory in function, acting via symmetric boutons typical of inhibitory synapses, and using the inhibitory transmitter GABA in at least the majority of their thalamic synapses.

The fact that outputs from the basal ganglia to certain thalamic nuclei are mainly or entirely inhibitory is compatible with the idea that the basal ganglia deliver signals that are important in imposing executive decisions, related to behavior and attentional focus, upon the CTH network. If the role of these inhibitory inputs *is* to release specific pieces of behavior, or foci of active attention, it follows that there should be a steady inhibitory "tone" from the basal ganglionic output nuclei, which is reduced or curtailed in selected connections, at specific times, to release specific pieces of behavioral activity or foci of attention. This has further implications:

i. The neural computations accomplished in the basal ganglia as a whole should also be concerned with behavior and other large-scale aspects of information processing, rather than with purely local computations (as is the case with the CTH network).
ii. Those CTH cell assemblies that *do* lead to behavioral output are likely, for most of the time, to be suppressed at the thalamic points of control by tonic inhibition. It is therefore likely that neurons in the basal ganglia output

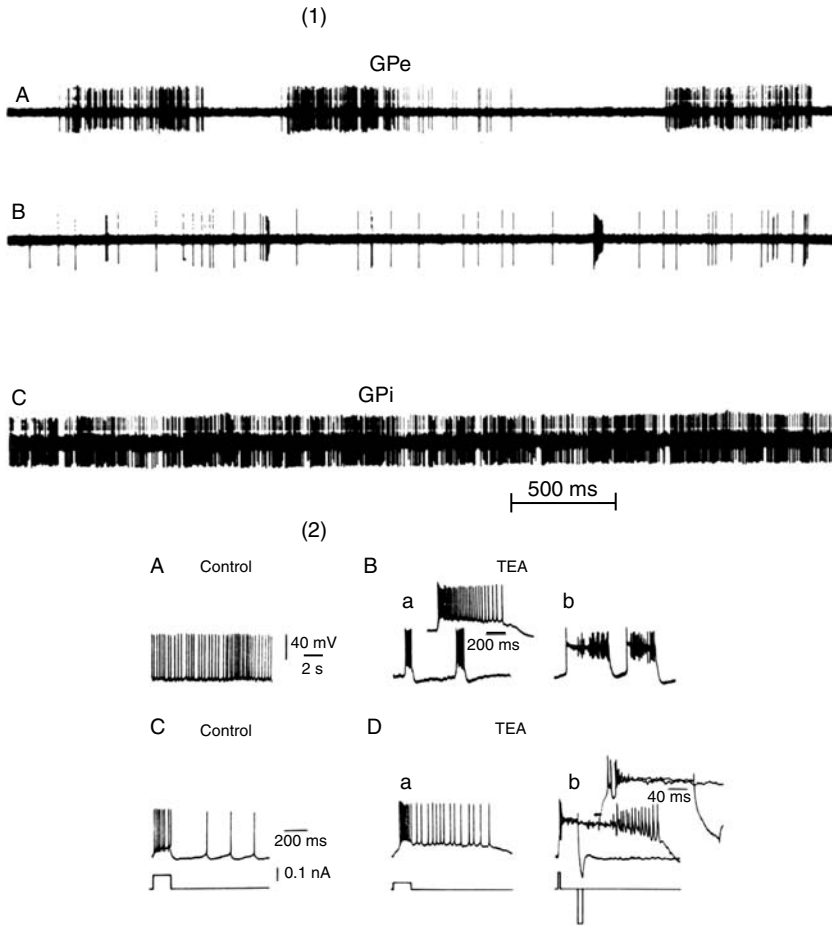


FIGURE 1.3 Tonic activity of neurons in basal ganglionic output nuclei in *in vivo* and in slice preparations. (1) Patterns of discharge seen in monkey pallidal segments at rest. (A) Unit with high-frequency discharge, broken by long periods of silence in GPe (typical of 85% of units recorded there). (B) Unit with low-frequency discharge, with bursts in GPe. (C) Unit with continuous high-frequency discharge in GPi. (From DeLong, M.R., *J. Neurophysiol.*, 34, 414–427, 1971. With permission.) (2) Units recorded in slice preparations of rat entopeduncular nucleus: (A) Spontaneous firing of unit; (B) Same unit during superfusion with medium containing tetra-ethyl ammonium ions (TEA; a: 10 mM; b: 20 mM) to block potassium currents. Spontaneous repetitive firing is replaced by phasic bursting; (C) Unit with little spontaneous firing, in which repetitive firing was evoked by a depolarizing pulse; (D) Same unit after superfusion with TEA. (Reprinted from Nakanishi, H., Kita, H., and Kitai, S.T., *Brain Research*, 527, 81–88. Copyright 1990, with permission from Elsevier.)

nuclei display tonic activity most of the time. This prediction is supported by the fact that neurons in the nuclei providing inhibitory connections with the motor thalamus (i.e., SNR and EP/GPi) are indeed tonically active (DeLong, 1971; Matsunami and Cohen, 1975; Anderson, 1977; Georgopoulos et al., 1983; Hikosaka and Wurtz, 1983a; DeLong et al., 1985; Cheruel

et al., 1994) (see Figure 1.3, part 1). The observation that the large inhibitory synapses in the motor thalamus derived from these nuclei are very rich in mitochondria (Kultas-Ilinsky et al., 1983; Kultas-Ilinsky and Ilinsky, 1990; Ilinsky Kultas-Ilinsky., 1997; see also the synapse labeled F_1, in Figure 1.2) suggests that they are metabolically very active, to be expected if their cell bodies are tonically active. This tonic activity (discussed in later sections) is certainly modulated by excitatory and inhibitory inputs. Nevertheless, rather regular continuous impulse discharge is seen in both SNR and GPi when studied in brain slice preparations, where such afferent influences are minimized (Nakanishi et al., 1987b, 1990; Nambu and Llinas, 1990) (Figure 1.3, part 2). Tonic activity thus seems to be an intrinsic property of the neurons in these nuclei, regardless of synaptic inputs. The fact that pallidal- and nigral-receiving neurons in the motor thalamus are exposed to tonic inhibitory activity from these sources does not in fact mean that these neurons are silent: Resting firing rates in pallidal-receiving zones of the motor thalamus in behaving monkeys have been reported to average 16 spike/s (Vitek et al., 1994). However, the activity in these neurons is probably not all concerned with behavior-related decisions, but with activity in other CTH assemblies, or nonspecific activity driven from the brainstem reticular formation.

iii. Any one of the neurons in the output nuclei can be expected to cease their firing only occasionally, and as part of specific small subsets of such neurons. Thus, a small number of neurons (components of CTH assemblies) all subserving related aspects of behavior or attentional focus can be released from inhibition together, at appropriate times. These are the times when past experience has demonstrated to the organism that the behavior they lead to is motivationally favorable. This brings us to consider the main input nucleus of the basal ganglia, the striatum, and its role in acquiring patterns of behavior that are motivationally favorable, and deploying them in appropriate circumstances.

If it is true that the basal ganglia are concerned with executive functions (decision making about which behavioral program to deploy, and which focus of attention to activate), another difference from the CTH network necessarily follows: In Section 1.1, it was mentioned that the accuracy of timing of impulses in the cortex (and probably elsewhere in the CTH network) was ~5 ms, determined by the integration time of a single pyramidal cell. This appears to be the unit in which the time is measured for the CTH network. However, behavior, and attentional focus are measured on a much slower timescale than this, often of the order of seconds or longer. One then suspects that the timescale of coding of information by the basal ganglia is a slower one than that in the CTH network. This implies that the principle for coding in the basal ganglia is quite different from that in the CTH network. This issue is revisited in Section 4.6.

2 The Striatum: Functional Significance and "Direct" Connectivity to Output Nuclei of the Basal Ganglia

2.1 THE STRIATUM: DETECTOR AND ENCODER OF MOTIVATIONALLY SIGNIFICANT OUTCOMES OF BEHAVIOR AND DEPLOYER OF MOTIVATIONALLY FAVORABLE BEHAVIORS

Figure 2.1 depicts, in schematic form, major connections of the basal ganglia. (This diagram is used as a template in later figures, where it is modified so that specific routes through the basal ganglia are highlighted.) The reader's attention is drawn to one feature, which immediately sets the basal ganglia apart from the cortex and other parts of the CTH network. In the CTH network almost all interconnections are reciprocal: If locus A projects to locus B, it probably also receives connections back from locus B. This is not the case with the basal ganglia: There is overall a unidirectional flow of signals (left to right in Figure 2.1) from the input nucleus (the striatum) to the various output nuclei (EP/GPi and SNR), which project to the motor thalamus. Admittedly there are some projections in a direction "against the flow," such as those from subthalamus (STN) to the external segment of the globus pallidus (GPe*) and striatum, and from GPe to the striatum. Nevertheless, the fact that the cortico-striatal pathways and those from GPi/EP and SNR to the motor thalamus are unidirectional makes this a genuine contrast with the CTH network.

Within the basal ganglia (on their input side) lies the striatum, the largest nucleus of the basal ganglia. It receives inputs from all regions of the cortex, and these make excitatory synapses with the principal neuronal type of the striatum, the medium spiny neuron (Parent and Hazrati, 1995a). The star-like array of dendrites of such neurons are densely covered with dendritic spines (see Figure 2.8, part 1), and it is upon these spines that the cortico-striatal axons make most of their synaptic junctions. These synapses are typical excitatory ones (with asymmetric membrane

* The external segment of the globus pallidus (GPe) has a different terminology in rodents—"pallidum" or sometimes "GP." Here the term "pallidum" is generally used when referring to rats.

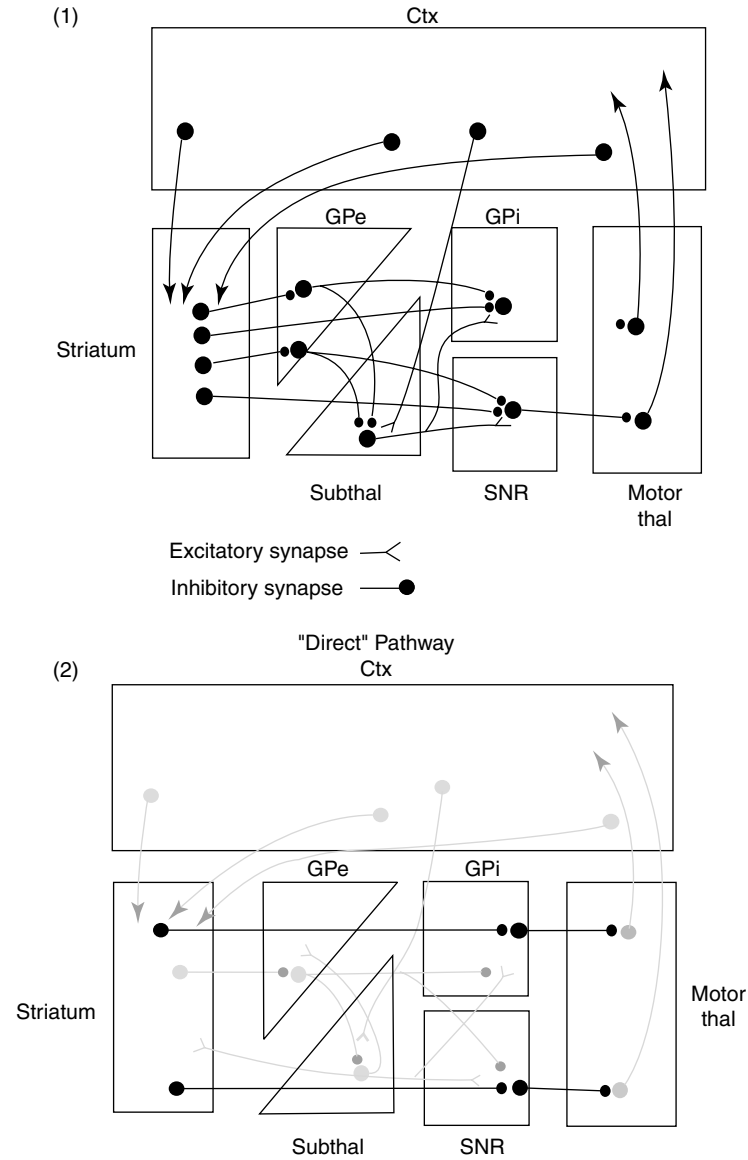


FIGURE 2.1 (1) Schematic illustration of main components and main connections of the basal ganglia. Main flow of signals through basal ganglia is from left (striatum) to right (motor thalamus). Other abbreviations: Ctx, cerebral neocortex; GPe/GPi, globus pallidus, external/internal segment; Subthal, subthalamus; SNR, substantia nigra pars reticulata. (2) Modified version of this figure emphasizing the "direct" pathway from striatum via GPi and SNR to motor thalamus. (*Note*: Other modified versions of this figure are used later to emphasize the different possible routes for the "indirect" pathway from striatum to motor thalamus.)

thickenings and round vesicles in the presynaptic bouton). The striatum is also well known as the structure in which the transmitter dopamine has a concentration higher (by far) than in any other part of the brain (Versteeg et al., 1976). Dopamine is known to be involved in the reward/reinforcement function implied by the rubric of instrumental conditioning (Crow, 1972; German and Bowden, 1974; Beninger, 1983). Various pathways control impulse traffic in the midbrain dopamine neurons (see reviews by Miller and Wickens, 1991; Miller, 2000b). These include motivational centers such as the amygdala and hypothalamus, which analyze motivational significance of sensory input, and use the outcome to control the dopaminergic system in reward-related learning. Recent evidence (Wickens et al., 1996; Reynolds et al., 2001) has shown that dopamine is an essential cofactor for a special type of synaptic strengthening in excitatory cortico-striatal synapses. The conditions for such synaptic strengthening appear to be similar to those for behavioral conditioning in the "self-stimulation" paradigm (Reynolds et al., 2001). Thus, as predicted more than 25 years ago (Miller, 1981) dopamine-mediated synaptic strengthening in the striatum appears to be the synaptic mechanism underlying reward-related behavioral conditioning. The details of the proposed rule for synaptic strengthening in the striatum are worth mentioning here. These are a modification of the rule proposed by Hebb (1949), thought to apply to synaptic strengthening in the cortex. Hebb's rule envisaged two factors—the coincidence of impulse activity on pre- and postsynaptic sides of a junction—as necessary and sufficient for synaptic strengthening to occur. In the formulation of Miller (1981), referring to the striatum, a third factor—a phasic pulse of dopamine release—was also necessary. The details of this "three-factor rule" have been examined more recently by Reynolds and Wickens (2002). The balance between the three factors becomes relevant in Part II of the present work (Chapters 9 and 10), when, in some disorders of the basal ganglia, dopaminergic tone becomes excessively high, and the requirement for concomitant increase in presynaptic neural activity becomes less than normal.

Dopamine exerts its actions by a variety of pharmacological receptor types. These fall into two families: the D1-like family (including D5 as well as D1 receptors), which, when activated by dopamine, increases the formation of cyclic adenosine monophosphate (cAMP); and the D2-like family (including D3 and D4, as well as D2 receptors), which has no effect on—or inhibits—cAMP formation. The effect of dopamine in strengthening of cortico-striatal synapses is mediated by the D1-like, not the D2-like dopamine receptor classes (Calabresi et al., 2000; Kerr and Wickens, 2001). In support of this, such synaptic strengthening is closely related to increased production of cAMP in striatal neurons (Colwell and Levine, 1995), which is normally achieved by activation of D1, not D2 receptors. These electrophysiological results follow a large body of psychopharmacological work examining the dopamine receptor upon which the reinforcement function depends. While this literature is exceedingly complex, it leads generally to the conclusion that activation of D1 receptors is involved more directly than that of D2 receptors (see reviews by Miller et al., 1990; Beninger and Miller, 1998). Correspondingly, measures, which increase cAMP production in the striatal complex, also enhance behavioral reinforcement effects (Miserendino and Nestler, 1995; Beninger et al., 1996), and reduction of the effects of cAMP reduces dopamine-mediated reinforcement (Sutton et al., 2000).

In Section 1.2, it was suggested that the signals conveying information about motivational significance (e.g., of recently emitted behavior) must be of a category quite different from the sensory signals, which are delivered to the cerebral neocortex. In fact, there is evidence that the dopaminergic signals to the striatum are indeed categorically different from those in sensory pathways: Analyses of striatal principal neurons have revealed that the dopaminergic axons make symmetric synaptic appositions with the medium spiny neurons (Freund et al., 1984). Approximately, two-thirds of the dopaminergic inputs to these neurons are situated on dendritic spines and about one-third on dendritic shafts with a minor input on cell bodies (Freund et al., 1984). This distribution probably reflects fairly the overall distribution of available dendritic membrane (Wilson, 1992). However, the above numbers can be incorrectly interpreted to indicate that the majority of spines receive a dopaminergic input. Although all spines are recipients of an asymmetric synaptic input (i.e., a cortico-striatal synapse), only ~8% also receive a second symmetric input (Wilson et al., 1983; Bennett and Wilson, 2000). There are additional sources of inputs to spines, which form symmetric contacts (see Bennett and Wilson, 2000), assuming that half of the symmetric inputs are dopaminergic, then only 4% of spines receive such input. The conclusion (though still debated) appears to be that if dopamine is involved as a modulator, mediating plasticity of other synapses (e.g., cortico-striatal ones), it is likely to be acting diffusely, rather than by making use of one dopamine release site for every synapse to be modified. This is quite different from the style of connectivity in major sensory and motor pathways, where information processing is considered to depend on point-to-point communication at a vast number of synapses.

In Section 1.3, it was argued that the inhibitory actions of the basal ganglionic output nuclei upon thalamic neurons imply that the basal ganglia are involved in executive processes, that is, in decision-making about behavior and attentional focus. Reinforcement processes impinging on the striatum and their relation to instrumental conditioning provide another important clue to this role of the basal ganglia. This follows, because instrumental conditioning and decision-making are closely related psychological functions: Decision-making *now* depends on instrumental conditioning *in the past*. What I chose to do now depends on my knowledge of which actions in the past have led to favorable or unfavorable outcomes. Thus, the evidence that the striatum is closely involved in instrumental conditioning is another indication that the basal ganglia deal with decisions related to behavioral output of the whole organism, rather than just with signals local to each neuron and with associations detected at each neuron, as in the cortex.

Further corroboration of this comes from studies of single-unit activity in relation to instrumentally conditioned movements, as well as stimulation and lesion studies in the striatum and the structures it influences. In the caudate or putamen (parts of the striatum, in primate species), or pallidum, unit firing does not have an exact temporal relation to motor acts, and, for delay tasks, it may anticipate them (Soltysik, 1975; Neafsey et al., 1978; Georgopoulos et al., 1983; Hikosaka et al., 1989a). Impulse firing in most neurons of the putamen is related to the intended direction of movement irrespective of load (assisting or opposing), and only ~13% have a pattern of activity closely related to actual muscle activity (Crutcher and DeLong, 1984; Alexander, 1987). The same is true in the arm areas of both segments of the pallidum (Mitchell

et al., 1987; Brotchie et al., 1991a). In addition, the pallidal-receiving parts of the motor thalamus do not produce simple motor movement when subjected to electrical microstimulation (Buford et al., 1996; Miall et al., 1998), although the cerebellum-recipient regions do so. Lesions of the pallidal-recipient regions of the motor thalamus cause severe impairment in instrumentally conditioned tasks, but this is not due to failure of the motor mechanisms of their execution (Canavan et al., 1989). These movements, as well as other skilled forelimb movements could be made adequately, but could not be carried out in the circumstances appropriate to each instrumental task. Taken together, these studies provide substantial evidence that impulse activity in the basal ganglia, including striatum, pallidum, and the regions of motor thalamus they influence, are related to behavioral programs with particular goals, rather than to motor coordination. The conclusion that the basal ganglia are concerned with behavioral control for the whole organism is necessary, because instrumental conditioning (unlike classical conditioning) involves feedback of the effect of the behavior of the whole organism upon a trace of the recently emitted behavior. The evidence of dopamine-mediated synaptic strengthening in the striatum indicates that it is in *this* structure that information about the effect of behavior is introduced into the basal ganglia. This determines the fact that, in the structures downstream from the striatum, including some cortical regions, neural activity also codes for intentions of behavior.

In the striatum, *in vivo* studies show that, as in the cortex, membrane potential may be bistable with both "down-states" and "up-states" (Cowan and Wilson, 1994; Stern et al., 1997). However, biophysical evidence from single neurons suggests that the mechanisms underlying such bistability differ between cortical pyramidal cells and striatal principal cells. In the cortex a major contributing factor to the "up-state" appears to be active dendritic sodium and calcium currents (Pockberger, 1991; Amitai et al., 1993; Kim and Connors, 1993; Regehr et al., 1993; Cauller and Connors, 1994; Schwindt and Crill, 1999), which can amplify the effect of a small number of synaptic excitations on parts of the dendritic tree distant from the soma. After such currents have brought membrane potential close to firing threshold, certain potassium currents may be rapidly opened to limit further depolarization (except temporarily when each impulse is generated) (Schwindt et al., 1988; Szente et al., 1988; Locke and Nerbonne, 1997). This stabilizes the membrane potential just beneath the firing threshold, and permits action potentials to be accurately timed with respect to current inputs (Carandini et al., 1996; Nowak et al., 1997). In the striatum the mechanism generating the up-state is different. There is evidence that convergent activation from very many coactive cortico-striatal fibers is needed to bring medium spiny neurons toward the point of firing (Wilson and Kawaguchi, 1996). Potassium currents are initially opened, thus limiting the depolarization produced, but they inactivate slowly after this, so that membrane potential may then "creep" slowly toward firing threshold (Nisenbaum et al., 1994). As a result, the time of firing of impulses is not exactly related to the timing of afferent synaptic excitations. Active dendritic currents have recently been detected in striatal principal cells (Kerr and Plenz, 2002), but these appear to have a different mode of operation, and probably a different functional role from those in cortical pyramidal cells.

From this evidence one can construct a rough model of how the basal ganglia as a whole mediate the acquisition and deployment of executive programs for active

behavior. The relevant pathways are highlighted in Figure 2.1 (part 2). Patterns of activity relayed from many widely distributed cells in the cortex to the striatum determine that striatal principal cells are brought to the up-state in which firing can occur. The cortical cells comprising each pattern acquire enhanced synaptic effects on striatal neurons, if the behavioral consequences of their becoming active (as a result of their downstream impact on the CTH network) turn out to be motivationally favorable. The most obvious way in which this might happen is if the downstream impact is to release from inhibiting a cell assembly governing some strategy of *active* behavior with favorable consequences. Specifically, activity in one (or a few) of the striatal inputs to EP/GPi or SNR should release activity in one (or a few) output fiber(s) from these nuclei to the motor thalamus. An alternative to this is that *suppression of activity* in an assembly, which would otherwise be activated, also has motivationally favorable consequences. This possibility is considered in Section 3.4.3. In terms of actual connections, for a cell assembly to be released from inhibition, it is necessary that the tonic activity, in particular, inhibitory links from the basal ganglia output nuclei to motor thalamus would themselves be inhibited. This scheme fits an important feature of the connectivity of the basal ganglia—the direct connections from the striatum to the inhibitory output nuclei themselves have inhibitory effects. This is well established both by the fact that striatal projection neurons are exclusively GABAergic (Ribak et al., 1979; Penney et al., 1986; Kita and Kitai, 1988) and by electrophysiological evidence that their influence on the output nuclei is inhibitory (Yoshida et al., 1972; Levine et al., 1974; Ohye et al., 1976; Tremblay and Filion, 1989; Kita and Kitai, 1991). Thus the patterns of cortical synaptic activity relayed to the striatum, which, by dopaminergic influences in the striatum become associated with favorable behavioral outcomes, can themselves exert their effects by inhibition of the tonic activity in selected inhibitory neuronal groups in the basal ganglia output nuclei. This reasoning from theory makes sense of the otherwise puzzling fact that two populations of neurons in sequence consist of inhibitory cells.

2.2 FUNCTIONAL SUBDIVISIONS WITHIN EACH COMPONENT OF THE BASAL GANGLIA

In Chapter 1, the term "executive function" was used to generalize between decision-making about outward behavior and that about attentional focus, not immediately expressed as behavior. In Section 2.1 of the present chapter the emphasis was on instrumental conditioning, seen as the means of acquiring outwardly directed purposeful behavior. However, there is a compelling body of experiment and theory suggesting that each component of the basal ganglia can be divided into subregions dealing, in a very broad sense, with widely differing domains of functions. This concept was first advocated by Alexander et al. (1986, 1990), on the basis of anatomical relations in the connections of the basal ganglia in primates. For instance, in the cortico-striatal projection, different regions of the anterior cerebral cortex projected with little overlap to different subdivisions of the striatum. Several such subdivisions of the striatum were thus identified. Other nuclei of the basal ganglia and motor thalamus could likewise be subdivided into components, related by their connectivity to subdivisions of the striatum and anterior regions of the cortex. The implication

was that not only in the striatum, but also in other components of the basal ganglia (GPe, GPi, and SNR) as well as the thalamus, there are subdivisions according to broad functional domains. The concept implicit in such anatomical parcellation is that there are several circuits through the basal ganglia, each of which has its representation in parts of each nucleus of the basal ganglia and motor thalamus.

It needs to be emphasized that the functional meaning of each of these circuits is defined in very broad terms, quite different from the segregated functional representation of different parts of the body, or the retina, in the classic sensory and motor pathways. Alexander et al. (1990) describe five such functional domains represented by basal ganglia–thalamocortical circuits: "motor" and "oculomotor" circuits, two "prefrontal" circuits (defined mainly in terms of connections, but tentatively related respectively to functions of short-term memory and switching behavioral set), and a "limbic" circuit (tentatively related to emotions and motivational processes).

The definition of these circuits as anatomically distinct has to be assimilated with the fact that, in each nucleus of the basal ganglia, the different subregions do not differ markedly in cytology or neurochemistry. For instance in the striatum, the cytology and chemoarchitecture of the caudate and putamen are much the same, with the limbic striatum showing only minor differences from these. One must then conclude that the basic computations accomplished in all parts of the striatum are also much the same. This can also be assumed for the subdivisions of each of the other nuclei (GPe, GPi, SNR, etc.). What differs, however, is the cortical regions of input to each circuit and the target regions of output to thalamus and back to the cortex (or brain stem). As a result, the exact computations accomplished in each nucleus, and in the basal ganglia as a whole, have to be described in rather abstract terms, such that it can generalize between the apparently very different psychological functions of each circuit (ranging from "sensorimotor control," through "behavioral selection," to "selection of attentional or motivational focus").

Such an abstract description can be based on a broadened definition of the term "behavior": Defining behavior as goal-directed purposeful strategies of action, one can distinguish micro- and macrobehavior, the former involving simple movements, perhaps involving just a single joint of the locomotor apparatus, and the latter involving locomotion and other whole-body movements. However, executive decisions about micro- and macrobehavior take place in the broader context of higher-level decisions about attentional and motivational focus. It is then possible to generalize between all of these, as steps in a hierarchy of behavior, with strategic decisions about ultimate goal, and focus of attention being taken first, then decisions about behavioral implementation of these goals (for instance, whether to "approach" or "avoid"), and, in the most immediate relation to goal fulfillment, tactical decisions about specific movements. In particular programs of behavior, these stages can be seen to be engaged dynamically in an "inward spiral" starting with broad strategic decisions about goals and ending with tactical ones leading to goal fulfillment.

The emphasis in many previous works on the basal ganglia, especially those on experimental primates, has been on sensorimotor aspects of function ("microbehavior"). In rodents it has been more common to investigate goal-directed behavior of the whole animal in relation to the basal ganglia. A notable advance in enlarging the concepts of function attributed to the basal ganglia in primates beyond the

sensorimotor domain was made by Grabli et al. (2004), who defined behavioral and cognitive manifestations arising in the nonmotor parts of GPe in macaque monkeys. This is referred to again in Part II of this book. Such widening of the concepts of basal ganglia functions are necessary if a unified account of the operations of these ganglia is to be constructed.

In the remaining parts of this chapter, and in Chapters 3 and 4 of Part I, the emphasis is to define, in generalized abstract terms, the roles of the different nuclei of the basal ganglia. This simplification neglects the contribution of the different subdivisions of each nucleus to each functional circuit, but is necessary in exposition of the large-scale operation of the basal ganglia. In fact, the arguments developed in these chapters *do* refer to specific functions, which, in principle, could be assigned to one or other functional domain or its corresponding circuit. Usually it is the domain of behavioral selection that is emphasized. The separate role of other functional circuits is not explored at this early stage of the exposition. It is implicit that the principles formulated in these chapters generalize to all functional domains and circuits. In Part II, in accounting for specific symptoms of disorders of the basal ganglia, the role of different functional circuits is given a more important role.

2.3 THE "CREDIT ASSIGNMENT PROBLEM"

If the scheme proposed in Section 2.1 is able to operate as envisaged, there are other more detailed morphological requirements for the connected structures of the basal ganglia. In the theory of control processes, there is an important issue, sometimes termed the "credit assignment problem" (see Marshall and Gupta, 1998). This is the problem of ensuring that, when favorable or unfavorable outcomes of a strategy of action appear, the credit (or "discredit") for this can be correctly assigned exclusively to the prior segment of action, which led to that outcome, rather than to other segments, which may have been emitted at about the same time. In fact, the credit assignment problem has both temporal and spatial aspects. The *temporal* aspect—ensuring that effects of behavior are assigned to those segments of a previous stream of actions occurring at the correct *time*—may be solved by assuming that synapses on active striatal neurons are susceptible to dopaminergic strengthening only within a narrow time window. This susceptibility, set up by prominent neural activity in striatal neurons, which lead to behavior, and referred to as the "state of readiness" (Miller, 1981), is envisaged to last for a duration of ~1 s. During this period, synapses in this state are eligible for synaptic strengthening if there is a phasic burst of activity in dopaminergic afferents. It has been suggested that the physical basis of the hypothetical "state of readiness" consists of brief elevations of the concentration of calcium ions within specific groups of striatal dendritic spines (Wickens, 1988).

The *spatial* aspect of the credit assignment problem arises because of the likelihood of divergence of neural pathways in the two or more synaptic relays between the striatum and the points in the thalamus, where CTH cell assemblies can be influenced. We thus need to consider the exact patterns of neuronal connectivity in the basal ganglia: Neurons of the CNS often have many thousands of output synapses, and in some macrostructures, such as the cerebral cortex, they appear to be distributed in a somewhat random fashion across many thousands of potentially recipient neurons

(Braitenberg and Schüz, 1998). The result is that most neurons in the vicinity, which receive *any* connections, receive only one, and far more rarely two or more. In such a network, as mentioned above, it is necessary that a number of afferents, from quite diverse sources, would have to activate the postsynaptic neuron at the same time to produce impulse discharge. Overall, the postsynaptic cortical neuron would then not have a very selective relationship with the firing of any one of the presynaptic neurons.

Consider the implications for programming instrumental behavior if such divergence/convergence applied to the connections from striatum to basal ganglia output nuclei, or from them to the recipient neurons of the CTH network in the motor thalamus. A severe problem would arise, because, in the network of connections over two (or more) synaptic relays from striatum to motor thalamus, divergence would be so great that patterns of activity relayed to striatal principal cells from the cortex could not control activity in the motor thalamus or cell assemblies in the overall CTH network with sufficient specificity to dictate any specific strategy of behavior. In this circumstance, there would be no mechanism whereby patterns of activity impinging on the striatum could be reliably identified with emitted items of behavior, which turned out to be motivationally favorable. Instrumental conditioning would not be then possible with the mechanisms and circuitry discussed so far. The cytological framework would be inadequate to solve the spatial aspect of the credit assignment problem. Thus a crucial question arises about the manner of connectivity between the striatum, the basal ganglia output nuclei, and the motor thalamus. Is the connectivity similar in style to that in the cortex or does it follow different principles?

2.4 MORPHOLOGICAL EVIDENCE ABOUT THE FINE DISTRIBUTION OF CONNECTIONS IN THE BASAL GANGLIA

Morphological evidence, which is presently available, is far from providing a complete answer to the above question. However, such evidence as is available suggests that the patterns of distribution of connections from one nucleus of the basal ganglia to the next (or to the motor thalamus) follow principles very different from those that apply in the cerebral cortex. First, the number of boutons of each striatal projection cell in output nuclei appears to be rather small, compared to those of the axons of cortico-cortical pyramidal cells. Thus, single striatal projection neurons in rat are reported to have arborizations in the pallidum with bouton counts of 80–220 (Kawaguchi et al., 1990). Those in the SNR are reported to have bouton counts of 62 ± 36 for one class of axons and 192 ± 79 for another (Wu et al., 2000), with boutons spaced at intervals of ~20 μm on their axon collaterals (see Figure 2.2, part 2). There appears to be no reports of bouton counts for striatal axon projections to the EP (GPi in primates), but since the general form of their arborizations is similar to those in GPe (Hazrati and Parent, 1992a–c), the bouton counts for single axons are probably similar to those in GPe. In contrast, in the mouse cortex, the axonal arborizations of cortico-cortical pyramidal cells have 7000–8000 boutons (Braitenberg and Schüz, 1998). Admittedly the projections of cortico-cortical neurons are shared between local collaterals and distant projections (with an estimated 50/50 split between local and distant arborization, according to Braitenberg and Schüz). Nevertheless, these

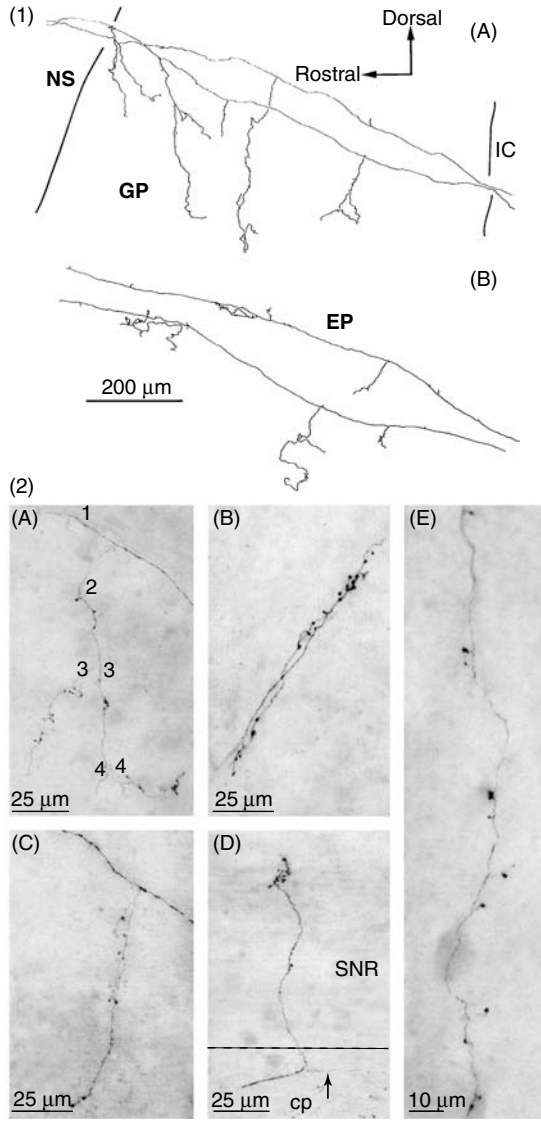


FIGURE 2.2 Morphology of single axon terminal arborization of striatal neurons projecting to pallidum or SNR. (1) Axon collaterals in pallidum (A) and EP (B) in rat (=GPe and GPi of primates) of striatal projection neurons labeled with biocytin. NS, neostriatum; IC, internal capsule. In (A), the two main labeled axons and their branches had, between them, 116 axonal varicosities. (Reprinted from Kawaguchi, Y., Wilson, C.J., and Emson, P.C., *J. Neurosci.*, 10, 3421–3438, 1990. With permission. Copyright [1990] by the Society for Neuroscience.) (2) Higher magnification photographs of axonal terminal branches (labeled with biocytin) showing axonal varicosities arising from striatal projection neurons of rat. Terminal branches are shown in pallidum ("GP": A and B), EP (C), and SNR (D and E). (Reprinted from Wu, Y., Richard, S., and Parent, A., *Neurosci. Res.*, 38, 49–62, 2000. Copyright [2000], with permission from Elsevier.)

authors find that boutons are spaced on average every 3–5 μm apart, much closer than on the arborizations of striatal projection cells. It must also be admitted that striatal output neurons may have arborizations in each of two- or three-component nuclei of the basal ganglia, and, within the striatum itself, they have their own rich distribution of collaterals. Nevertheless, this evidence suggests overall that, in terms of the morphology of connections, striatal projection neurons make far fewer synaptic contacts in the few structures to which they project, than do cortico-cortical neurons in their projection areas.

An even more important difference between arborizations of striatal output neurons and those of cortico-cortical neurons is the detailed manner of innervation of their target neurons. Striatal terminal projections to neurons in target nuclei are arranged in a fashion favoring the possibility of a single axon making multiple synaptic contacts with a particular neuron in the output nuclei. Thus striatal projections enter the pallidum (both GPe and GPi) as myelinated axons perpendicular to the disk-like dendritic trees of the intrinsic neurons, and give off fine unmyelinated collaterals at right angles (Figure 2.2, part 1), then running roughly parallel with the dendrites of the recipient neurons (Hazrati and Parent, 1992a,b). The fine arbors made by these collaterals are highly specific, so that striatal injections in closely neighboring points have nonoverlapping terminations in the pallidum (Hazrati and Parent, 1992b). Collections of such collaterals then run as a sheath surrounding and parallel to each dendrite. A single collateral makes repeated synaptic junctions (see Figure 2.3). In quantitative terms, each collateral gives several (1–10) synapses to the dendrite whose course it follows (Yelnik et al., 1996). Since several (e.g., four) collaterals from the same axon stem may accompany the same dendrite,

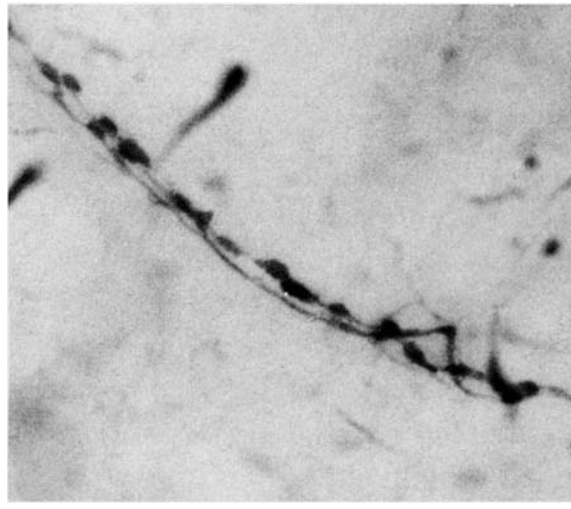


FIGURE 2.3 Photograph of multiterminal innervation of pallidal dendrites by striatal afferents. (Reprinted from Hazrati, L.-N. and Parent, A., *Brain Res.*, 598, 311–315, 1992. Copyright [1992], with permission from Elsevier.)

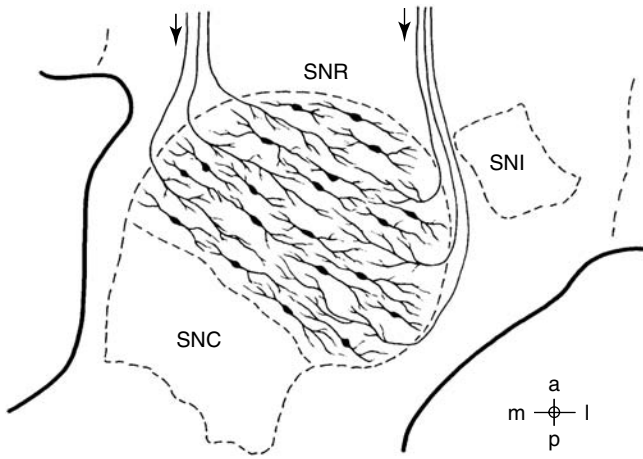
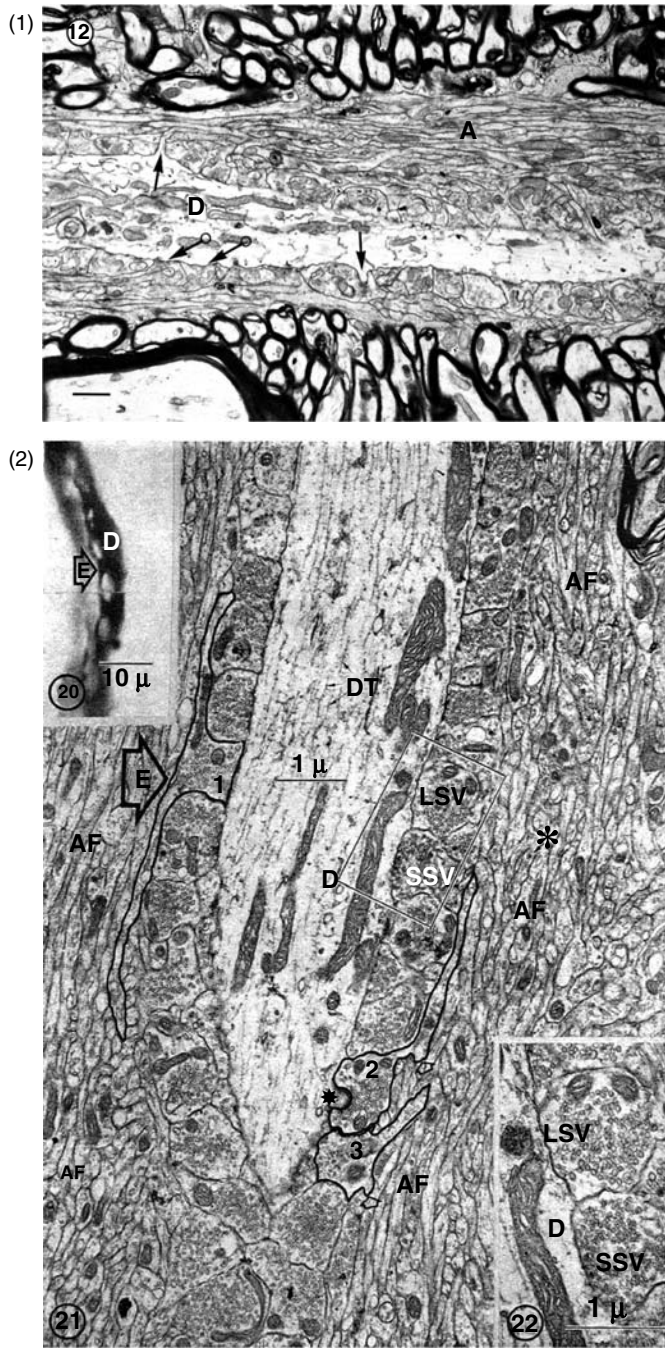


FIGURE 2.4 Diagram of striatal fibers approaching SNR and interleaving with dendritic fields there. (Reprinted from Tokuno, H., Nakamura, Y., Kuno, M., and Kitao, Y., *Neuroscience*, 38, 255–270, 1990. Copyright [1990], with permission from Elsevier.)

a single axon may make ~20 synaptic contacts upon a single pallidal dendrite. A very similar arrangement on a fine scale is described for striatal fibers entering the SNR (Schwyn and Fox, 1974; Rinvik and Grofova, 1970; Tokuno et al., 1990), although these fibers are unmyelinated as they enter this structure, and thus are not perpendicular branches from myelinated axon stems (Figure 2.4). In the electron microscope (Figure 2.5), one sees dendrites of neurons in GPi or SNR completely covered with synaptic boutons. Outside this layer of synapses there are many fine unmyelinated axons, running roughly parallel to the dendrite, and seen (in favorable circumstances) to be the axons supplying many synaptic boutons. In both structures the arrangements are examples of what Cajal (1934, 1954) called "longitudinal axodendritic terminations" (exemplified by cerebellar climbing fibers). In contrast, in the cortex, there is no such geometric arrangement, which could favor multiterminal innervation, and, from detailed study, Braitenberg and Schüz (1998, p. 88) are led to conclude, "the influence of one neuron onto another is weak, being mostly represented by a single synapse."

The questions of the number of boutons and the manner of their termination may also be asked with reference to connections from the basal ganglionic output nuclei to the motor thalamus. Some numerical data on bouton counts, based on single axon labeling studies in rat have been reported (Kha et al., 2000, 2001), including details of two populations of axons of EP cells projecting in the thalamus. One such population (exemplified by three labeled axons) projected only to the motor thalamus and had small terminal arbors there with a few varicosities (mean of only six) and fine axons. The other (four labeled axons) had larger terminal arbors with plentiful varicosities (mean 90) and coarse axons, giving off varicosities in VL/VM but projecting also to other structures. Axons projecting from the SNR to the thalamus had bouton counts in VM ranging from 45 to 223. In monkeys, Parent et al. (2001) report on


(1)
12
A
D
(2)
D
E
20
10 μ
DT
AF
1 μ
LSV
E
1
AF
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SSV
AF
2
3
AF
AF
LSV
D
SSV
1 μ
21
22

a similar study in which pallidal axons terminate in the motor and other nuclei of the thalamus with a somewhat larger number of axonal varicosities. Though these counts are quite diverse they are very much smaller than bouton counts for cortico-cortical pyramidal cells.

The exact manner of termination of axons from the basal ganglionic output nuclei within the motor thalamus is different from that of both striatal output axons or of cortico-cortical projections. Axons from the GPi within the thalamus of primates give rise to five to eight "extremely dense bunches" of axonal arborization (Arecchi-Bouchhioua et al., 1996, 1997; see also Parent et al., 2001) (Figure 2.6). Each bunch has dimensions of ~100 μm in height and 50–150 μm in rostrocaudal extent, and covers a group of 17–20 thalamic principal cell bodies. The number of boutons in each bunch is not specified, but the illustration in the 1996 paper (Figure 2.6, inset) suggests ~50 in a bunch (compatible with data reviewed in the previous paragraph in rat). Likewise, in monkeys, Parent et al. (2001) illustrate a pallidal axon terminating in motor thalamic nuclei with 8 "extremely dense bunches of terminals" and a total of 237 terminals, giving a mean of ~30 terminals per bunch. In principle, these might be distributed not only on the 17–20 cell bodies they encompass, but also on dendrites of other thalamic principal cells, which penetrate the region of the bunch. However, since ultrastructural studies show that the large inhibitory-like terminals derived from the basal ganglia are found mainly on proximal dendrites of motor thalamic principal cells (Kultas-Ilinsky et al., 1997; Ilinsky, and Kultas-Ilinsky, 1997; Sidibé et al., 1997), the latter possibility is unlikely. If so, these terminals are probably located mainly on the 17–20 neurons within the bunch. Whether these provide multiterminal innervation of a single neuron by each axon or one-to-one connectivity is not clear.

The above cytological data acquire more significance when combined with data on neuron numbers in the various components of the basal ganglia. In the rat there are ~100 times as many neurons in the striatum (2.8 million) as in the combination of the two output nuclei (~30,000) (Oorschot, 1996). If a single striatal output fiber provides ~100–200 synaptic boutons in each of GPi/EP or SNR neuron (as suggested above), the two output nuclei combined should receive ~2.8–5.6 $\times$ 10^8 synapses or ~10,000–20,000 synapses per neuron on average. Assuming that there are six dendrites per GPi/SNR neuron in the output nuclei (Iwahori and Mizuno, 1981; DiFiglia et al.,

FIGURE 2.5 Electron micrographs of GPi and SNR from monkeys in both studies. In both cases, the dendritic surface (D in both [1] and [2]) is covered in synaptic endings. Peripheral to this in each figure are plexi of many fine afferent axon collaterals (A in [1]; AF in [2]), running mainly in the same direction as the dendrites, some of which (ringed arrow in [1]; bold outlines in [2]) are seen to be in continuity with the synaptic endings. In GPi but not SNR the myelinated main axonal stems are seen, orthogonal to and outside the fine axon collaterals. Also shown in (2, upper left) ("20"): oil emersion light microscope picture of dendrite (D: right) making multiple synaptic contact with fine axon collateral (left). One such contact (E) can be compared with the synaptic contact shown in the main figure outlined with ink. Lower right ("22"): enlarged view of rectangle from main figure to show terminal boutons filled with small round vesicles (SSV) and large vesicles (LSV). ([1] From DiFiglia, M., Pasik, P., and Pasik, T., *J. Comp. Neurol.*, 212, 53–75, 1982. With permission from Wiley; [2] From Schwyn, R.C. and Fox, C.A., *J. Hirnforsch.*, 15, 95–126, 1974.)

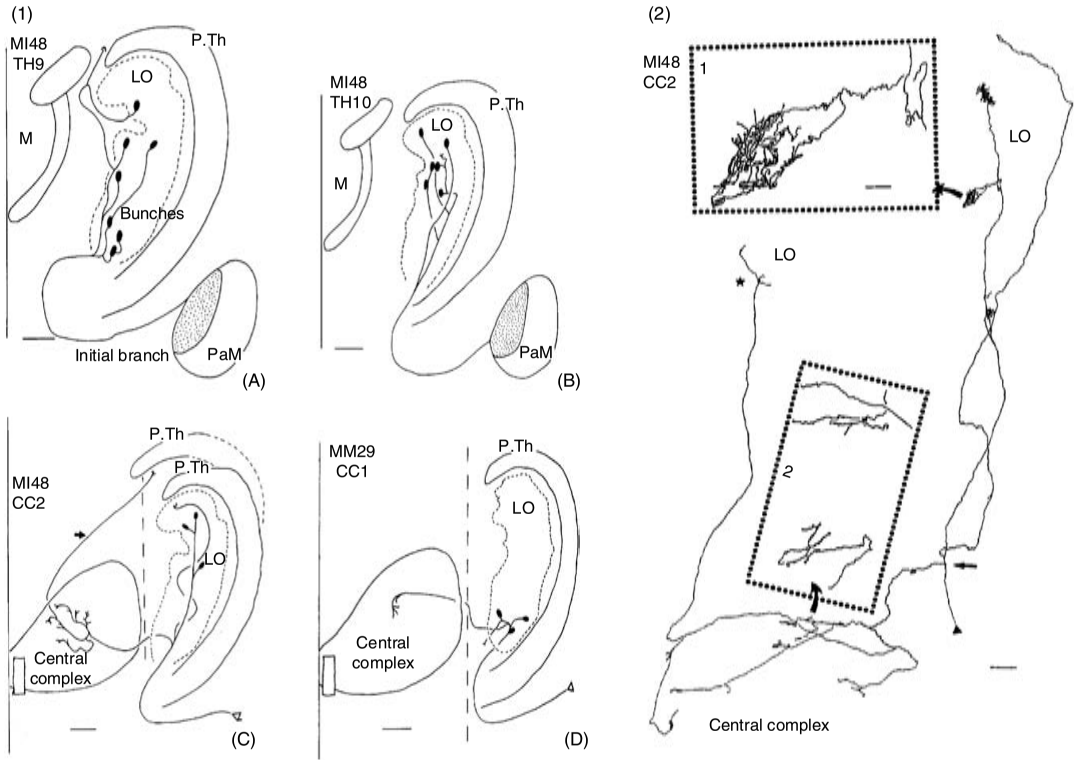

FIGURE 2.6 (1) Semischematic illustration of distribution of "extremely dense bunches" of terminal arborizations of four reconstructed axons in primate pallido-thalamic projections. PaM, medial pallidum showing tracer injection site (dotted). LO, thalamic nucleus lateralis oralis (broken lines). (2) Camera lucida drawing of single axon in lateral thalamus labeled from an injection site in medial pallidum (scale bar = 200 μm) with (inset 1) a single bunch seen at high magnification (scale bar 50 μm). (Reprinted from Arecchi-Bouchhioua, P., Yelnik, J., François, C., Percheron, G., and Tande, D., *Brain Res*., 754, 311–314, 1997. Copyright [1997], with permission from Elsevier.)

TABLE 2.1
Synopsis of Quantitative Synaptology of Striatal Projection to a Typical Pallidal Neuron in Rat

Multiterminal Innervation

(1) 1–10 terminals from a single axon collateral on a single dendrite
(2) Approximately, four collaterals from the same axonal stem accompany each pallidal or nigral dendrite
(3) Therefore, probably ~20 synapses *in toto* from one striatal cell synapse on one SNR or GP cell

Number of Striatal Cells Afferent to Each GP/SNR Cell

(4) Striatum contains ~3 million projection cells
(5) Each gives 100–200 synapses in the structure(s) it innervates
(6) Therefore, GPi+SNR receive 300–600 million inhibitory synapses (multiply [4] and [5])
(7) Together, GPi and SNR have ~30,000 cells (Oorschot, 1996)
(8) Therefore, each cell receives ~10,000–20,000 inhibitory synapses ([6] divided by [7])
(9) Therefore, with 20-fold multiterminal innervation, each cell in GPi/SNR receives inhibitory connections from 500 to 1000 striatal cells ([8] divided by [3])

1982; Yelnik et al., 1984), one can conclude that each such dendrite receives 1666–3333 input synapses. Assuming further that ~20 synapses from a single striatofugal axon converge on a single neuronal dendrite (see Section 2.4), each dendrite will receive input synapses from 83 to 166 striatal projection neurons. Each neuron will receive its full tally of input synapses from 500 to 1000 striatal cells. This seems large, but, compared with the cortex, the number of striatal cells afferent to each neuron in the target nuclei is actually rather small: Single cortico-cortical pyramidal cells, with ~7000–8000 output synapses, distribute these synapses mainly one to each recipient neuron, with very little multiterminal innervation (Braitenberg and Schüz, 1998), which means that each pyramidal cells makes synaptic contact with up to 7000–8000 other cortical cells. This quantitative argument is summarized in Table 2.1.

2.5 CYBERNETIC INTERPRETATIONS DERIVED FROM QUANTITATIVE SYNAPTOLOGY

What can we conclude from this analysis of connectivity? For the basal ganglia, the corollary is that each striatal neuron has a rather strong influence on any of the neurons in the output nuclei with which it makes synaptic contact. Probably, therefore, little convergence of inputs from several such neurons is required to be fully effective in inhibiting its target. Thus, although each GP, EP, or SNR neuron can be influenced by many striatal neurons, *any one* of the latter, if active, can, by itself dictate that the tonic activity in the recipient neuron is silenced. (This argument is, at present, to some extent a conjecture: To make the argument more rigorous, one

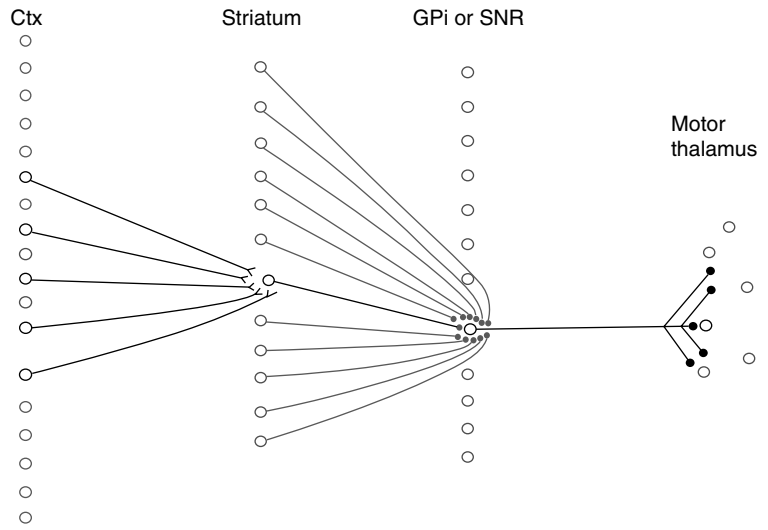

FIGURE 2.7 Diagrammatic synopsis of connectivity in "direct pathway" from cortex, through striatum, and GPi/SNR to motor thalamus (illustrating concept of "alternative labeled lines" of connectivity). All links are meant to represent connections which exist in anatomical terms. (It is implied that all the neurons in the striatum receive input connections from the cortex similar to those shown; and similarly, that all neurons in GPi/SNR or motor thalamus receive inputs from their respective afferent structures, similar to those shown.) Neurons, activity in which it is necessary and sufficient for transmitting behavior-related signals from cortex (through striatum and pallidum) to a specific neuron in the motor thalamus, are drawn in bold lines.

also needs to know the electrotonic length of GPi/EP or SNR and neurons, to assess the effectiveness of distally placed synapses. No studies published to date provide such data.)

Moreover, since the number of neurons in basal ganglionic output nuclei is small, the total number of output lines from the basal ganglia to the motor thalamus (and thence to the CTH network) is also relatively small. However, the number of afferent lines to these output neurons from the striatum is quite large, and it appears likely that any one of these afferent lines can, by itself, exert decisive control of one or more output neurons, without much convergence between neurons being necessary (see Figure 2.7). Thus there are very many ways in which information represented in the cortex and conveyed to the striatum can be used to control the relatively limited number of basal ganglionic output lines.

Recently, there has been much debate about whether connectivity from the cortex, through the basal ganglia, to the motor thalamus uses a large number of parallel lines, or alternatively a progressive "funneling" of information, as signals are relayed across a sequence of nuclei with progressively smaller numbers of neurons (e.g., Parent and Hazrati, 1995a). This dichotomy arises from consideration solely of anatomy. When, however, the anatomy is viewed in relation to possible physiological interactions, a resolution of an otherwise perplexing issue, arising from

the foregoing discussion, becomes possible, as follows (Figure 2.7): The *striatum* is indeed a nucleus where funneling occurs, since every medium spiny striatal neuron receives very many excitatory afferent synapses from cortex (and thalamus), and requires considerable convergence among coactive afferents in these populations to bring the neuron to threshold for firing (Wilson and Kawaguchi, 1996). In the *projection from striatum to the output nuclei*, each neuron in these nuclei also receives connections from a large number of striatal neurons (though by no means as large as the number of cortical neurons, which can influence another cortical neuron). However, unlike the cortico-striatal projection, any one of the striatal axons to a neuron in the output nuclei can provide decisive control over that neuron, without need for convergence between coactive afferents. In this sense the pathways from striatum to output nuclei correspond to a large number of alternative lines of control (even though morphologically there is great convergence). This arrangement is an important part of the solution to the spatial aspects of the credit assignment problem.

The idea that, in pathways between striatum and motor thalamus, the connectivity amounts to independent labeled lines receives support from electrophysiological studies. When several neurons are recorded simultaneously from the globus pallidus of awake behaving monkeys, the cross-correlation histograms (CCHs) for neuron pairs are almost always flat, with very little evidence that the neurons receive a common input (Nini et al., 1995; Bar-Gad et al., 2003). This is in striking contrast to neuron pairs recorded in frontal cortex or thalamus, and suggests parallel lines of connectivity with little or no interaction.

The same principle probably also applies to the pathways from the basal ganglionic output nuclei to the motor thalamus. This principle would again appear to be necessary if the constellations of active cortical inputs recognized by the striatum are to be used for executive control. However there is a significant difference. In the pathway from striatum to output nuclei, neural activity in most of the inhibitory striatal neurons is low (see Section 3.4.5), and the few cells which are more active are presumed to "take the initiative" by silencing the tonic activity in specific cells in the output nuclei. In morphological terms many such cells converge on single output neurons, but in physiological terms it is likely that only one at once is involved in silencing each of the critical cells in the output nuclei. However, in the projection from output nuclei to motor thalamus, most afferent cells have high levels of tonic activity. Thus, if projections from several cells in the output nuclei provide inhibitory input to each cell in the motor thalamus, silencing the tonic activity *in any one of them* will not release the cell into activity, because inhibitory tone is maintained by others. Hence, if the arguments presented so far are correct, and the basal ganglia are principally concerned with acquiring and deploying programs of instrumental behavior, a very specific prediction can be made: Each neuron in the motor thalamus receiving inhibitory inputs from the output nuclei should receive these inputs from just a single cell in the output nuclei. In other words the "extremely dense bunches," which form the terminal arborizations in the projection to the motor thalamus, should consist of one or more "baskets," each uniquely connected with the proximal dendrites of a single thalamic cell, with no anatomical convergence. Presently available evidence is compatible with this prediction, but is not yet sufficiently

specific to establish it. Already, we have evidence from connectivity in other parts of the basal ganglia for specialization to solve the credit assignment problem implicit in the rubric of instrumental conditioning. However, this additional specialization in connectivity to the thalamus is a further requirement if that problem is to be fully overcome.

Of course, if the credit assignment problem is to be fully solved, active cell groups in the striatum have to be able to address not only specific cells in the motor thalamus, but also, eventually, specific behavioral output. It is not envisaged that there will be specific labeled lines all the way from the striatum to lower motor neurons of the brain stem and spinal cord, or even to the upper motor neurons of the motor cortex. If that were the case, when activity in the striatum controlled behavior, it would control the exact motor expression of the behavior rather than, as a generality, the goal of the behavior. Rather, the striatum, via specific cells in the motor thalamus, addresses cell assembly configurations each of which is distributed throughout the CTH network. These are formed as a result of all instrumental conditioning accomplished at earlier times in the animal's life, and represent all the many ways in which each goal can be mapped against motor performance. For example, a rat trained to obtain food by running a maze, still retains the habit when the maze is flooded and the rat has to swim. Thus single neurons in the motor thalamus should represent goals, not movements. As such, they *must* be addressed specifically by activity in striatal cells.

One of the deeper issues regarding the function of neural tissue in the CNS, relevant also in understanding the connectivity of the basal ganglia, is whether pathways function as specific "labeled lines." This concept had its origin in the study of sensory systems as the doctrine of "specific nerve energies" put forward in the early nineteenth century by Müller (see, e.g., Dethier, 1978). The concept implies that pathways convey specific information because they run in parallel without major interaction. In the cortex, that vast associative network, this concept does not apply. In major sensory pathways to the thalamus, there is considerable evidence that it does apply. Thus, in the visual and somatosensory pathways to the thalamus there are separate lines of transmission for each submodality, and there is precise topographical relationship between points on a sensory surface and points at each level of the pathway (e.g., retinal ganglion cells or relay cells of the dorsal column nuclei). Functionally, the precise topography is likely to be maintained or sharpened as a result of surround inhibition in these relays (Gordon, 1973). The connections of the basal ganglia afferents to the motor thalamus also appear to use labeled lines, although, from the preceding discussion this consists of a large number of *alternative labeled lines* converging on to a small number of points of control of CTH network. Another difference from sensory pathways is the use of "longitudinal axodendritic terminals" to ensure that a single afferent line can by itself exert control over a recipient neuron. This arrangement may be necessary, because surround inhibition (typical of sensory pathways to the thalamus and serving to "sharpen" the topographic relationships defined by the excitatory connections) makes sense only when the basis of information transmission is via excitatory connectivity, but is meaningless when information transmission is mediated by inhibitory synapses.

2.6 COLLATERAL INHIBITION IN THE STRIATUM

There is another corollary of these arguments, which throws further light on the cytology of the striatum: From the foregoing theory, it is likely that, of the many striatal neurons which are able to control basal ganglionic output neurons, only a few should do so at any one time, otherwise clear executive decisions cannot be taken. Studies in behaving monkeys support this inference. Neighboring medium spiny neurons, although firing in relation to movements of the same part of the body, show enormous variability related to the exact parameters of the task and the overall context in which the movement occurs. Firing may be specifically related to whether the movement is spontaneous, memory-guided, or triggered or guided by a stimulus, the nature of the stimulus, and whether or not the movement has behavioral significance (Schultz and Romo, 1988; Hikosaka et al., 1989a,b; Alexander and Crutcher, 1990; Alexander et al., 1992). From this evidence it seems likely that in unanesthetized animals, at any one moment, rather few cells are active.

Such arguments suggest that there must be some means of limiting the number of striatal medium spiny neurons, which are active at any one time to just those which define a particular strategy of behavior with favorable outcome. One of the possibilities makes use of the fact that medium spiny neurons in the striatum distribute axon collaterals among neighboring neurons. These collaterals are likely to be inhibitory in function (Figure 2.8), since their neurons are GABAergic. The implication here is that, when striatal medium spiny neurons are in the up-state and are generating action potentials, their local collaterals should distribute inhibitory influences that limit the number of such neurons, which can be active in a locality at the same time.

Empirically, however, the role of collateral inhibition in the striatum has been a matter of controversy. Two early studies were in favor of such inhibition. In one, in urethane-anesthetized rats, depolarizing currents, which triggered action potentials in medium spiny neurons, were reported also to produce subsequent inhibition in the same neuron (Park et al., 1980). It was concluded that recurrent inhibition, some of which was directed to the same neuron that had activated the inhibition, occurs in the network of medium spiny cells. In another study bicuculline (antagonist of the transmitter GABA) was delivered iontophoretically in the neighborhood of recorded striatal cells to block inhibitory processes. This made more probable the occurrence of depolarizing shifts from around firing threshold to a level some way positive of threshold (Calabresi et al., 1990). This suggests that in the up-state when many neurons are firing, there is normally some GABAergic restraining influence, perhaps that of local inhibitory collaterals. However other studies have failed to demonstrate collateral inhibition. Wilson et al. (1989) showed in striatal slice preparations that antidromic activation of medium spiny output neurons was not accompanied by any IPSPs comparable to those produced by antidromic activation of cortical pyramidal cells. Orthodromic stimulation from the cortical inputs could be adjusted so that small subthreshold EPSPs were produced, but not action potentials. Under these conditions, IPSPs were still seen. Thus action potentials in medium spiny neurons (and presumably their collaterals) were neither necessary nor sufficient for producing IPSPs. It was concluded that the inhibition, which was seen, was of a feed-forward rather than

a feedback nature, mediated by cortical influences to local inhibitory interneurons, rather than by the medium spiny principal cells. Similarly it has been shown in slice preparations from rat nucleus accumbens that fornix stimulation could be adjusted so that IPSPs but not EPSPs were produced (Pennartz and Kitai, 1991). This is again evidence for feed-forward (rather than feedback) inhibition in this part of striatum. Dual intracellular recording experiments in striatal slices from neuron pairs within 50–200 μm of each other have failed to demonstrate mutual inhibition (Jaeger et al., 1994). In later experiments *in vivo* Jaeger et al. (1995) performed cross-correlation analyses of spike trains from simultaneously recorded pairs of neurons. There was no evidence of any sort of interaction, including inhibitory interaction. All these results cast doubt on an assumption, widely made in theoretical accounts of the striatum, that neighboring striatal cells can inhibit each other.

The issue has been recently reinvestigated in dual intracellular studies (Tunstall et al., 2002). Mutual inhibition *could* be seen (Figure 2.8), but was weak, and best seen with extensive signal averaging. Mean amplitude of these unitary IPSPs was 277 μV (range 157–319 μV). From a sample of 45 neuron pairs, only ~10% of the 90 possible inhibitory connections were actually demonstrated. Similar GABAergic influences between neighboring medium spiny neurons have been reported by Czubayko and Plenz (2002) in organotypic cultures of striatal tissue and by Taverna et al. (2004) in slices from the nucleus accumbens. The proportion of neuron pairs in which such influences could be detected was somewhat higher than in the study of Tunstall et al. (2002) amounting to 15–40% in the study of Czubayko and Plenz, and 34% in that of Taverna et al. Nevertheless, these influences were present in only a minority of neighboring neuron pairs. In morphological terms, each medium spiny neuron both gives to and receives from its neighbors a large number of synaptic connections. Individually it appears from such experiments that these connections have small but detectable inhibitory effects. Thus, when medium spiny neurons are actively generating impulses, there may be a mechanism by which they can *collectively* distribute substantial levels of inhibition to their neighbors. Between *individual* neurons in an arbitrarily selected pair of neighboring neurons, however, the probability of such an influence is low.

Since the reversal potential for GABAergic synaptic effects is that of a chloride potential (around −60 to −70 mV), some way positive of the resting membrane potential of striatal neurons in the down-state, their net effect could be to activate recipient medium spiny neurons (see Czubayko and Plenz, 2002). In the up-state, when membrane potential is above the chloride equilibrium potential, they are likely to mediate inhibition between neighbors. These inhibitory influences could thus play a part in limiting the *total* number of such neurons, which are active at any one time. Even considered collectively, however, this inhibition can easily be overridden: Thus, in barbiturate-anesthetized preparations, when there are strong cortical rhythms of neural activity, coherent among large populations of cells, large rhythmic fluctuations in membrane potential in striatal neurons, sometimes with action potentials superimposed at the peaks, occur in phase with electroencephalographic (EEG) rhythms in the cortex. These are presumably also coherent over large populations of striatal cells. Even when the striatal cells discharge action potentials during the up-state, the peaks in striatal membrane potential are undiminished by any collateral

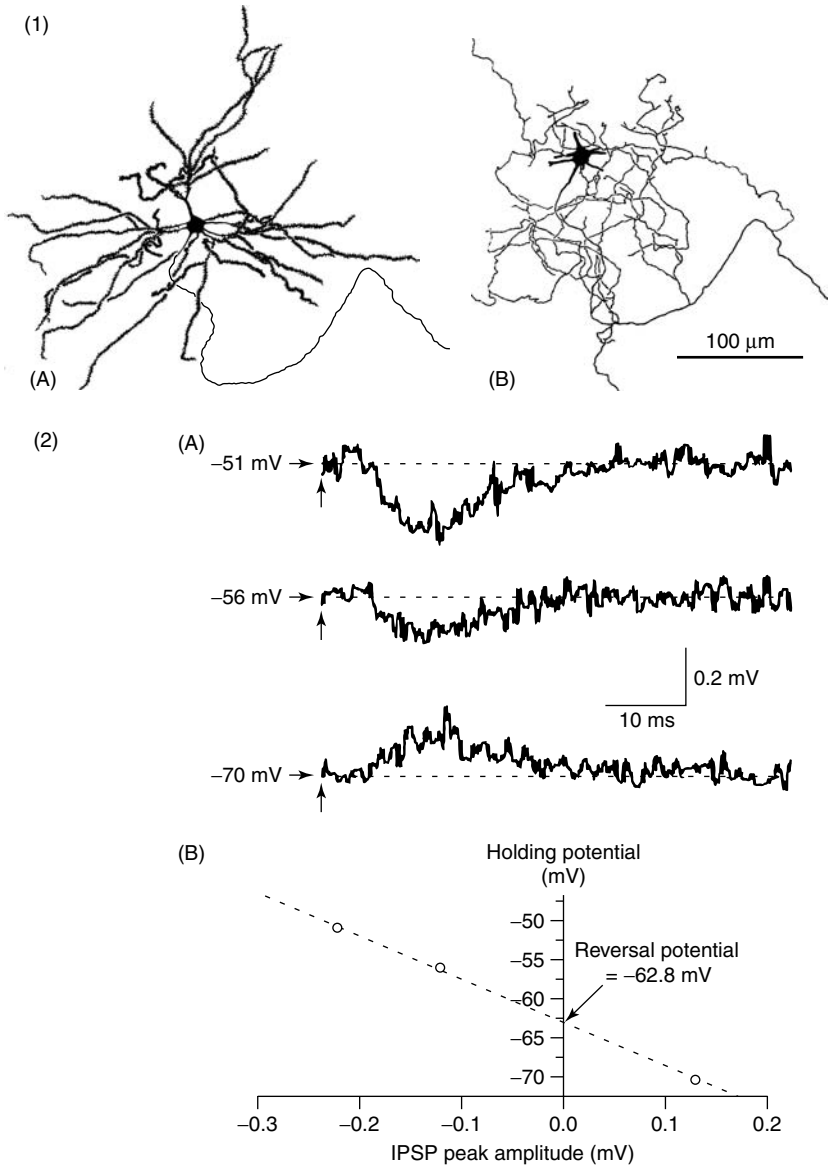

FIGURE 2.8 Soma and dendritic tree of a striatal medium spiny neuron labeled by intracellular injection of horseradish peroxidase, and electrophysiological evidence of collateral inhibition between neighboring cells of this sort. (1) Neostriatal spiny projection neuron showing dendritic arborization (A) and local axonal arborization (B). (From Wilson, C.J. and Groves, P.M., *J. Comp. Neurol.*, 194, 599–615, 1980. With permission from Wiley.) (2) (A) IPSPs produced in one medium spiny neuron by stimulation of another in experiments involving dual intracellular impalements. Each trace is the average of 200 successive responses. Sign of the averaged IPSP reverses as membrane potential is shifted between −51 and −70 mV. (B) Graphical presentation of results to show reversal potential. (From Tunstall, M.J. et al., *J. Neurophysiol.*, 88, 1263–1269, 2002. With permission from *Journal of Neurophysiology*.)

inhibition between neighbors (Charpier et al., 1999). Similar results have been obtained in ketamine-anesthetized rats (Goldberg et al., 2003). Striatal neurons also fire in correlation with cortical rhythms after dopamine depletion of the striatum, as studied in urethane-anesthetized rats (Tseng et al., 2001a), again implying coactivation of neighboring neurons. It has also been reported for urethane-anesthetized rats (Magill et al., 2006) that during slow-wave electrocortical activity, pallidal unit firing gives evidence of multiple convergence from activity in striatal recording sites, but when the EEG is activated, functional convergence on pallidal neurons was no longer apparent. The latter situation, it is suggested, represents the use of "alternative labeled lines," as proposed for awake behaving animals.

What does this mean for the deployment of strategies of instrumental behavior and the exercise of executive decision-making functions by the basal ganglia? At any one time, impulse traffic in a cluster of a small number of medium spiny neurons can exert specific control over which cell assembly in the CTH network is released into activity and releases behavior. There can be many different clusters that can exert control over any one control point in the motor thalamus, each to be used at different times. The small number of basal ganglionic output lines is probably quite adequate, bearing in mind the vast potential of their coming-to-be-controlled by different constellations of cortical activity, and in different combinations to target different CTH cell assembly groupings. The members of each cluster are selected by dopaminergic reward processes: They are those which were active immediately prior to the emission of a piece of behavior which had favorable consequences. The cortical afferent synapses to such neurons are then reinforced, so these neurons tend to become active together as a cluster. All this is possible because of the "alternative labeled line" morphology in the basal ganglia output pathways: The credit assignment problem is solved by this distinctive style of connectivity. In addition, the "activity control" mediated by collateral inhibition in the striatum ensures that in most circumstances, striatal activity is kept confined to that cluster, despite wide fluctuations in the overall levels of cortical input to the striatum. Behavioral evidence for the normal presence of such restraining inhibitory tone in the striatum is provided by Scheel-Krüger (1983) in experiments where microinjection of a GABA antagonist into the striatum of rats led to locomotor stimulation, and (in some regions) rearing and stereotyped sniffing, licking, and biting.

Within the patterns of connectivity in the basal ganglia characterized as "alternative labeled lines," it is still likely that each instrumental program is represented by a number of different lines, rather than just a single labeled line. This follows from the facts that, even with the "activity control" mechanism, active cortical cell assemblies would activate a number of striatal cells, individually too far apart to be influenced by collateral inhibition. Thus, there would also be a number of control points in the motor thalamus at which a particular CTH cell assembly could be accessed as a result of activity in these striatal cells. Consequently, connectivity for lines of information transmission during a specific piece of instrumental behavior can be characterized as "multiple point-to-point," with no interaction between the multiple labeled lines until they reach the motor thalamus and CTH network.

Inhibitory influences, which can limit activity in striatal medium spiny neurons, reflect not only feedback from activity in such neurons, but also potent feed-forward

inhibition derived from a class of GABAergic striatal interneurons, as implied by Wilson et al. (1989). Such feed-forward synaptic effects on medium spiny cells are more potent than the feedback effects exerted via axon collaterals of medium spiny cells (Koós and Tepper, 1999; Tepper and Bolam, 2004). Moreover, the GABAergic interneurons appear to be connected electrotonically (Koós and Tepper, 1999; Tepper et al., 2004), suggesting that they form a syncytium capable of exerting large-scale control over striatal activity. What controls the firing of such interneurons is not well understood, although it has been shown that they receive potent excitatory inputs converging from functionally diverse areas of cortex (Ramanathan et al., 2002), and recurrent inhibitory inputs from the pallidum (=GPe) (Bevan et al., 1998). These interneurons may mediate extrinsic control over striatal activity, rather than the self-limiting control envisaged for the inhibitory collaterals.

3 The "Indirect" Pathways from Striatum to Basal Ganglia Output Nuclei, and Their Relation to the "Direct" Pathway

3.1 OVERALL PATTERNS OF CONNECTIVITY

The main emphasis of Chapter 2 was the functional relation between the striatum and the motor thalamus as determined by the *direct* pathways from striatum to the basal ganglia output nuclei. An essential part of the argument was based on the fact that there is a sequence of two inhibitory links in typical pathways between striatum and motor thalamus. However, there are other important pathways not included in the analysis so far (see Figures 2.1 and 3.1). For instance, the striatum projects not only to EP (GPi in primates) and SNR, but also to the pallidum (as called in rats; GPe in primates). The latter structure gives no direct projections to the motor thalamus. It does, however, project to both the EP or its equivalent (Smith et al., 1988; Hazrati et al., 1990; Hazrati and Parent, 1992c), SNR (Totterdell et al., 1984), and the subthalamus (STN). Pathways have also been described projecting from GPe back to the striatum (Staines et al., 1981; Arbuthnott et al., 1982; Beckstead, 1983; Staines and Fibiger, 1984; Kita et al., 1999). Subthalamic nucleus (STN) also receives a significant input direct from the cerebral cortex, especially its motor and premotor regions rather than its granular sensory regions (Künzle and Akert, 1977; Künzle, 1978; Monakow et al., 1978; Rinvik et al., 1979; Afshapour, 1985; Canteras et al., 1990; Nambu et al., 1996). Such projections take their origin from cortical lamina V (Canteras et al., 1990). The subthalamus in turn also sends projections to both the aforementioned output nuclei as well as to both GPe (pallidum in rats) (DiFiglia et al., 1982; Hazrati and Parent, 1992a,c) and the striatum (Kita and Kitai, 1987; Carpenter and Jayaraman, 1990; Smith et al., 1990b).

Many routes for information flow are permitted by these pathways. Some connections internal to the basal ganglia are reciprocal. However, several key pathways are *not* reciprocated by connections in the opposite direction. These nonreciprocal pathways are those from cortex to striatum and STN, from STN to EP/GPi and SNR, and those from EP/GPi and SNR to motor thalamus. Thus, despite the complexity, it remains true that the striatum and the subthalamus are principal input nuclei of the basal ganglia; and EP/GPi and SNR are principal output nuclei.

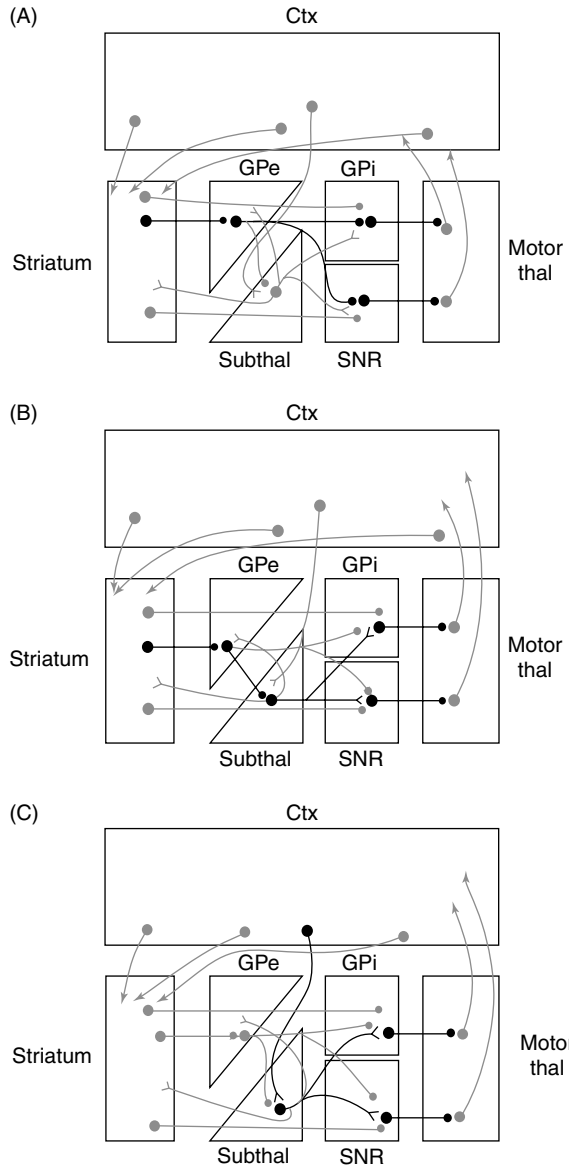

FIGURE 3.1 Schematic illustration of main connections of the basal ganglia emphasizing different versions of the "indirect" pathway (connections in bold). (A) Indirect pathway through GPe and GPi/SNR (avoiding subthalamus); (B) indirect pathway through GPe, subthalamus, and GPi/SNR; and (C) indirect pathway from cortex to subthalamus and GPi/SNR.

Given this, the various pathways between striatum and output nuclei involving GPe are sometimes referred to as the *indirect* pathways (Figures 3.1A and 3.1B) to distinguish them from the direct pathways from striatum to output nuclei (Figure 2.1). The basic connectivity suggests two versions of this pathway: First, there are pathways from GPe direct to GPi or SNR (Figure 3.1A). Alternatively, there could be pathways from GPe to STN, and thence to GPi and SNR (Figure 3.1B). Functional evidence to be considered below helps to resolve the status of these two versions of the "indirect pathway." Prior to this more detailed discussion, the term will be used in its most familiar fashion to refer to pathways from striatum to the outflow nuclei via GPe, whether or not the subthalamus is involved. An additional and equally plausible route for information flow is from cortex to subthalamus, and from there to several other parts of the basal ganglia (striatum, GPe, GPi, and SNR) (Figure 3.1C).

Beyond evidence about connectivity, there are important points to be discussed relating to the "sign" of the various connections, that is, whether they are excitatory or inhibitory: The principal neurons of GPe are inhibitory (GABAergic) (Carpenter, 1981; Ribak et al., 1979; Ottersen and Storm-Mathisen, 1984; Beckstead and Kersey, 1985; Smith et al., 1987, 1990a) and so inhibit neurons in the subthalamus and output nuclei to which they project. Those of the subthalamus are glutamatergic (Albin et al., 1989; Smith and Parent, 1988) and excitatory (Robledo and Féger, 1990; Kita and Kitai, 1991), and so excite neurons in output nuclei as well as those in the GPe and striatum to which they project. Cortico-subthalamic projections (like cortico-striatal ones) are excitatory. Thus, in the pathways from striatum to GPe to output nuclei to motor thalamus there is a sequence of *three* inhibitory links. In those from striatum to GPe to subthalamus to output nuclei to motor thalamus, there is a sequence of two inhibitory links, one excitatory link and then another inhibitory link. These various pathways, conventionally included under the term "indirect pathway," have the same "net sign," that is, a total of three inhibitory links (three reversals of sign). Alternatively, one could consider pathways from cortex to subthalamus to output nuclei to motor thalamus as containing two excitatory links and one inhibitory link (a "net sign" of one inhibitory link). Another possible route for information flow is from cortex to subthalamus to GPe to output nuclei to motor thalamus (a "net sign" of two inhibitory links).

With these facts about the sign of individual links within the basal ganglia and the complexity of the connections themselves, it is clear that the concept of two inhibitory links in pathways between striatum and motor thalamus applies to only some of the possible routes for signal transmission. Attention of recent theorists has focused on the different roles of the so-called "direct pathways" from the striatum with two reversals of sign, and the "indirect pathways" with three reversals. If striatal neurons control behavior, those from which the direct pathway originates would have a "net sign" of influence over behavior which is the opposite of those from which the indirect pathway originates. Activity in the former and latter class of striatal cells would *release* and *suppress* active behavior, respectively. A similar statement can be made with respect to other functional domains dealt with by other circuits through the basal ganglia, referring to release of foci for attentional or motivational targets. Thus, it is of some theoretical importance whether the direct and indirect pathways from the striatum arise from neurons that are strictly segregated or are to some extent in common.

3.2 SEGREGATION VERSUS OVERLAP OF "DIRECT" AND "INDIRECT" PATHWAYS FROM STRIATUM TO THALAMUS

This issue has been investigated with several techniques and in several species. The most commonly used technique involves retrograde labeling with different tracers injected into different projection nuclei. To answer whether neurons projecting to direct and indirect target nuclei are strictly segregated or overlap to some degree, it is necessary that the injection sites in the different nuclei are targeted by the same general region of the striatum, whether or not from the same neurons. It is also necessary that an injection into the pallidal complex does not indiscriminately cover both GPi (EP in rats) and GPe (pallidum in rats), otherwise the possible segregation of neurons of origin of the direct and indirect pathways will be obscured. When these conditions are met, experiments in cats (Beckstead and Cruz, 1986) and primates (Féger and Crossman, 1984; Selemon and Goldman-Rakic, 1990; Giménez-Amaya and Graybiel, 1990; Flaherty and Graybiel, 1993a) generally find that few (<5%) labeled neurons are retrogradely labeled from both direct and indirect target nuclei. Neurons projecting to the different target nuclei show some clustering, but are nevertheless closely intermingled. Cells with each type of projection are roughly equal in numbers, but are not confined to separate regions. In rats however, 40% of retrogradely labeled striatal neurons were double-labeled from both targets, with single labeling from SNR and pallidum in 40% and 20% of neurons, respectively (Loopuijt and van der Kooy, 1985). Possible errors due to technical problems with these methods were discussed by Beckstead and Cruz (1986) and Selemon and Goldman-Rakic (1990). The discrepant result in rats has not been replicated. It depends on the assumption that the label injected into pallidum was not taken up by axons passing through this structure on the way to SNR. In addition, since target areas in rat are much smaller than those used in the other species, they are more easily loaded so heavily with tracer that relatively minor projections might be detected and given undue weight. A more recent double retrograde labeling experiment, where different microspheres were injected into SNR and pallidum of rats (Santiago and Potter, 2001), found that only 4% of labeled neurons in the striatum were double-labeled.

Another technique, used in a few studies, is to label single projection axons, and then reconstruct their trajectory, including branch pattern and terminal arborizations. This is most easily done in rats, where up to 60% of striatal projection axons have arborizations in target nuclei of both the direct and indirect pathways (Kawaguchi et al., 1990; Wu et al., 2000). Recent evidence (Parent et al., 1995; Lévesque and Parent, 2005) shows similar collateralization in primates, with bouton-rich arborizations of most striatofugal axons being found in both GPe and GPi/SNR. (About 25% of the total bouton number for these axons were counted in GPe.) In cats, evidence of collateralization was found using electrophysiological methods (Yoshida et al., 1972), where monosynaptic inhibition of pallidal neurons was found from axon collaterals of caudatonigral fibers. This method, like the method of single axon tracing, focuses on a very few axons, and may give a less accurate overall view of quantitative aspects of the respective projections.

Another commonly accepted point of contrast between neurons of origin of the direct and indirect pathways (as defined above) is that they contain different

neuropeptides. This conclusion was initially based on comparison of tissue in GPe with that in either SNR or GPi using immunochemical assay or staining for various neuropeptides. It has generally been found that the neuropil in the target nuclei for the direct pathway (GPi or SNR) contains high levels of substance P (SP) and/or dynorphin (DYN), while that in the target nucleus of the indirect pathway (GPe) contains high levels of enkephalin (ENK)* (Haber and Elde, 1981; Graybiel, 1986; Reiner et al., 1999). The difference between nuclei of the direct and indirect pathways is not, however, an absolute categorical one. In histological studies, the inner part of GPi stains moderately for ENK and strongly for SP, and GPe stains sparsely for SP and intensely for ENK (Haber and Elde, 1981; Marshall et al., 1983; Graybiel, 1986; Reiner et al., 1999; Mounir and Parent, 2002). Some of the ENK in GPe may derive from neurons intrinsic to that structure, rather than from striatal projections (Voorn et al., 1999). SNR contains many ENK-positive processes (Marshall et al., 1983). A comparative study (Inagaki and Parent, 1984) showed that the specificity of SP/DYN (rather than ENK) labeling in SNR was noteworthy in rats and cats, but not in primates. In immunochemical assays in human brain tissue, levels of DYN in GPe, though lower than those in SNR, are still significant (~20% of those in SNR according to Dawbarn et al. [1986]; ~50% according to Seizinger et al. [1986]).

More precise details of the striatum are provided by studies at the cellular level. In retrograde labeling studies with concurrent immunocytochemical identification of peptides, neurons of the direct pathway have been reported to contain SP and DYN, but not ENK, while those of the indirect pathway contain ENK but not the other peptides (Gerfen and Young, 1988; Flaherty and Graybiel, 1993a). When striatal tissue is immunostained for both SP/DYN and ENK, some studies find a very low level of colocalization (Anderson and Reiner, 1990; Le Moine and Bloch, 1995). However, in other studies a substantial proportion of striatal cells were double-labeled to an extent expected from the proportions of neurons labeled with either marker, assuming random rather than segregated labeling (Penney et al., 1986; Besson et al., 1990). Graybiel (1986) reported that SP-labeled striatal neurons may also label for ENK, if colchicine is given to block axonal transport (thus permitting accumulation of ENK within the somata). Nadjar et al. (2006), with a sensitive immunolabeling method, found that in monkey, as many as 92% of striatal cells projecting to GPi labeled for DYN and 51% for met-ENK. Of those projecting to GPe, 65% labeled for met-ENK and 86% for DYN. These authors suggest that they may have overestimated the degree of colocalization due to the high sensitivity of their method. However, it appears to be an exaggeration to claim strict segregation.

Another approach to determining whether striatal neurons of origin of the direct and indirect pathways are separate is to inject the "suicide toxin" volkensin into different target nuclei in rats, with resultant destruction of the striatal neurons of origin of projections (Roberts et al., 1993). When injected into SN, the density of striatal neurons staining for SP was reduced significantly more than that of those staining for ENK. When injected into the pallidum, the difference (again significant) was in the opposite direction (greater loss of ENK-staining neurons).

* The functional role of the respective peptides has not been clarified, and will not be discussed in further detail here.

Summing up the evidence on neuropeptides, labeling of striatal neurons for SP/DYN and ENK appears to some degree to be segregated; these neurons projecting respectively to the nuclei of the direct and indirect pathways. However, this is not an absolute categorical separation, and may reflect merely quantitative differences and the limited sensitivity of the various staining methods. Taking evidence using all the techniques just discussed, there is considerable evidence that neurons of origin of the direct and indirect pathways are segregated. An earlier suggestion that in rodents the two populations show considerable overlap was not supported by a more recent double labeling experiment. However, from single-axon tracing experiments, it is not completely resolved if these two populations overlap to some degree. Whether this issue is critical depends on the theory of basal ganglionic function, which can be derived from a wider range of evidence. We return to this in Section 4.5 (see first footnote).

3.3 THE "CREDIT ASSIGNMENT PROBLEM" IN THE INDIRECT PATHWAY

Another significant cytological finding is that the projections of GABAergic cells in GPe to both the output nuclei (GPi and SNR) have very specific patterns of termination: Many inhibitory boutons from a single GPe axon are clustered around the cell body and proximal dendrites of GPi or SNR cells as pericellular "baskets" (Hazrati et al., 1990; Bevan et al., 1994; Sato et al., 2000). There is also electrophysiological evidence that the IPSPs produced in GPi by stimulation of GPe are very large ones (Kita, 2001) to be expected from this morphological appearance. In view of the arguments in subsections of chapter 2 (Sections 2.3 through 2.5), this morphological arrangement suggests that "labeled lines," with little need for functional convergence from different axons in the relay from one nucleus to another, as found in the direct pathway, are also found in these connections of the indirect pathway. If this inference is correct, it implies that the pathways from GPe to GPi and SNR, like those from the striatum direct to the latter two structures, are designed so that specific programs for behavior can be addressed from the striatum via these routes in the indirect pathway as well as those in the direct pathway.

However, neurons of GPe, like those of GPi or SNR, but unlike those of the striatum, have high levels of tonic activity. If there is anatomical convergence from neurons in GPe to those in GPi or SNR, it will be impossible for reduced activity in a single afferent line to lead to restoration of tonic activity in selected neurons of these output nuclei, because other GPe inputs with tonic activity will sustain the inhibition. Therefore, if specific programs are to be addressed from GPe, unlike striatal fibers projecting to the output nuclei, fibers projecting from GPe to the output nuclei should not be *alternative* labeled lines, but characterized by strict one-to-one transmission, as suggested above for the pallidothalamic pathway (and for the same reason). The existence in GPi and SNR of pericellular baskets of inhibitory connections derived from GPe axonal projections is suggestive of this arrangement (although not proving it). There may be divergence, such that each of several axonal branches of a GPe neuron makes individual contact with each of several neurons in GPi or SNR, but there should not be convergence.

Following the reasoning in Section 2.5, for the projection from output nuclei to neurons of the motor thalamus, one can then also predict that the number of neurons in GPe projecting to the two output nuclei should be the same as, or less than the number of neurons targeted in these nuclei, but should not be more. Empirical data exist with which to assess the plausibility of this prediction. According to Oorschot (1996), the number of neurons in rat pallidum is ~46,000, and that in EP plus SNR sums to ~30,000. In all these nuclei there are some interneurons, whose numerical proportion has never been estimated, but is generally thought to be small. In addition, GPe contains neurons projecting back to the striatum. It is suggested that these make up as many as 30–40% of GPe cells (Kita and Kita, 2001). Thus, while it is by no means proven that forward-projecting neurons in GPe equal in number the projection neurons in GPi + SNR, it is plausible to suggest that this is the case.

3.4 EVIDENCE ON THE RELATIVE ROLE OF "DIRECT" AND "INDIRECT" PATHWAYS

The fact that outflow pathways from the striatum appear to be divisible into two roughly equal portions—the so-called "direct" and "indirect" pathways—whose "net sign" of influence on the motor thalamus are the opposite of one another raises substantial theoretical questions, whose elucidation is likely to throw important light on the operations of the basal ganglia as a whole. However, the evidence on connectivity, which provided the basis for this distinction, left questions about whether the pathways involving the STN (Figure 3.1B) were really part of an indirect pathway. An alternative view is that STN is an input nucleus for the basal ganglia, additional to the striatum, with afferent control from restricted parts of the cortex (Figure 3.1C). This complex issue is discussed first (Sections 3.4.1 and 3.4.2), leaving the evidence pertaining to the role of direct versus indirect pathways to be dealt with in Section 3.4.3. A fourth subsection (Section 3.4.4) deals with a complication, namely, the suggestion that dopamine, acting via different dopamine receptors, can have opposite effects on neurons of origin of the direct and indirect pathways. This concept has been widely regarded as important in understanding the difference between direct and indirect pathways, but, as argued below, does not withstand close scrutiny. With this issue out of the way, a more substantial issue can be dealt with (Section 3.4.5), the direction of change in firing rates in striatal neurons of origin of the direct and indirect pathways in relation to active behavior versus behavioral suppression.

3.4.1 Is the Subthalamus an Input Nucleus for the Basal Ganglia or a Relay in the Indirect Pathway?

The idea that there is a genuine pathway for information flow from GPe to STN to the output nuclei can be questioned on morphological grounds from evidence of Carpenter et al. (1981). They reported that in monkey, STN neurons projecting to the GPi arise from cells in parts of the STN different from those which receive projections from any part of GPe. However, such a segregation was not noted in rat (Smith et al., 1990a; Shink et al., 1996).

To understand whether STN is an essential part of the indirect pathway, it is necessary to compare the effects of various manipulations on firing rate in STN and other parts of the supposed indirect pathway. If STN were part of an indirect pathway from GPe to the output nuclei of the basal ganglia, receiving inhibitory connections from the former, excitation in GPe should be accompanied by inhibition in STN. Moreover, changes in STN should occur *after* (i.e., with longer latency than) those in GPe. In contrast, if excitatory influences from STN to GPe are influential, increase in firing in each of these two nuclei should be associated with shorter latency in STN than in GPe. These two possibilities are not mutually exclusive and there is evidence in favor of both predictions.

Much of the relevant evidence has been obtained from study of the effects of cortical stimulation on unit firing in STN and GPe. Ryan and Clark (1991) stimulated two regions of cortex (prelimbic and agranular frontal cortex) in rats. This produced, in units of GPe, an initial excitation (of 6 ms latency) followed by a short period of inhibition (starting at 15 ms) and a late excitation (latency of 29 ms). In response to the same stimuli, STN neurons showed an early excitation whose latency was slightly earlier (starting at 4 ms) than that in GPe, suggesting that the early excitation in GPe resulted from excitatory transmission from STN. After this, there followed an inhibitory period (at 9 ms) and a late excitation (at 16 ms). Similar observations were made by Nambu et al. (2000) in monkeys. Stimulation of cortical forelimb regions of the primary motor/sensory region (M1/S1) induced in GPe a short-latency excitation followed by a period of inhibition and a long-latency excitation. The same phases of response were seen in STN, but, as in the experiments of Ryan and Clark, the early excitation had a shorter latency than that in GPe.

Ryan and Clark (1991) also showed that kainate lesions of STN prevented the excitatory responses in GPe, further evidence that the latter were initiated via STN. Similar observations were made by Nambu et al. (2000): Blockers of the excitatory amino acid *N*-methyl-D-aspartate (NMDA), but not non-NMDA glutamate blockers, introduced into STN, attenuated both the early and the late excitation in GP. Muscimol, a GABA agonist, introduced into STN blocked all activity there, and abolished both the early and the late excitation in GPe. In these two studies, the duration of intermediate-latency inhibition in GPe was also greatly increased by STN lesion or blockade. Presumably, this inhibition was initiated via pathways from cortex to striatum, which were more potent when competing excitation from the subthalamus was removed.

In experiments in behaving monkeys, it was found by Georgopoulos et al. (1983) that movement-related increases in neural activity in STN neurons began earlier with respect to movement than those in GPe. Likewise in a lever-press task, Cheruel et al. (1996) found that excitatory responses in STN were triggered with shorter latency than those in GPe. These results are not compatible with a predominantly inhibitory control of STN from GPe, but rather with excitatory control in the opposite direction. Furthermore, in ketamine-anesthetized rats, increased firing of pallidal units occurs at the same time as striatal neurons show up-state membrane potentials with superimposed unit firing (Goldberg et al., 2003). This is not compatible with the view that the striatum exerts inhibitory control of pallidal neurons in this preparation, and is best explained in terms of excitatory control from the cortex, exerted both on the striatum, and via STN, on the pallidum.

Notwithstanding such evidence of excitatory subthalamic control of GPe, other evidence points to inhibitory control of the subthalamus by GPe. The intermediate-latency inhibition in STN seen by Ryan and Clark (1991), which had shorter latency than that in GPe, probably had its origin in the undiminished firing of GPe cells, prior to striatal inhibition of these cells. Fujimoto and Kita (1993) also reported two excitatory peaks in STN, interrupted by a brief period of inhibition. Excitotoxic lesions of the striatum did not abolish the two excitatory responses, while ibotenic acid lesions of GPe abolished the short intervening periods of inhibition. Further functional evidence for significant inhibition of STN from GPe comes from Ryan and Clark (1992). They found that excitotoxic lesions of GPe in rats caused an increase in the proportion of STN cells responding to the stimulation of the frontal agranular cortex and an increase in the duration and magnitude of STN responses. They also showed that lesion of GPe caused an increase in frequency of firing in STN cells and a change to burst firing. That the inhibition from GPe to STN was under striatal control was suggested by the fact that lesions of the neostriatum produced some opposite effects (decrease in firing rate and response duration). Thus, STN appears normally to be under some degree of tonic restraint from GPe, and can be disinhibited by the striatum. Further evidence of disinhibition mediated by the striatum was obtained by Maurice et al. (1998). They stimulated the prelimbic/medial orbital part of prefrontal cortex in rats (a region linked to STN by both a direct route and an indirect one via the striatum). As in other studies, this produced two excitatory peaks in STN often separated by a brief inhibitory period. The late excitatory response was no longer seen after NMDA blockade in nucleus accumbens or GABAergic blockade in the ventral pallidum, suggesting that it reflected disinhibition via the limbic part of the striatum rather than direct excitation from the cortex. Behavioral evidence for a role of inhibition from GPe, exerted within STN, comes from experiments referred to by Scheel-Krüger (1983), showing that microinjections of the GABA antagonist picrotoxin into STN produce sedation.

Overall, such evidence demonstrates that GPe is subject both to excitatory control via cortex and STN and inhibitory control via the striatum; and likewise that STN can be controlled both directly from the cortex, and, via a trisynaptic disinhibitory pathway from the striatum and GPe. The evidence of control via striatum and GPe is compatible with the conventional "indirect pathway" from striatum via GPe and STN to the output nuclei of the basal ganglia.

A last body of evidence, correlational in nature, should be considered to evaluate the involvement of STN in the so-called "indirect pathway": If STN were indeed part of an indirect pathway from GPe to the output nuclei of the basal ganglia, receiving inhibitory connections from the former, firing rates of neurons in GPe and STN should change in *opposite* directions under a variety of influences. In contrast, if the excitatory links from STN to GPe are more influential, one might also expect firing rates in the STN and GPe to change *in parallel*, or for changes in STN neurons to occur out of proportion to those in GPe neurons. One would also expect parallel (rather than opposite) changes in GPe and GPi (at least in some circumstances), since both of these receive excitatory influences from STN.

Several studies favor the second of these two alternative patterns. Urbain et al. (2000) found that, across the sleep–waking cycle, GPe and STN neurons show

parallel changes, both increasing firing rate on transition from waking or slow-wave sleep to rapid eye-movement sleep. Two studies show parallel changes in GPe and GPi after manipulation of STN, suggesting the importance of excitatory connections to both structures in determining firing rate. Hamada and DeLong (1992) showed that subthalamic lesions in monkeys produced parallel falls in firing rate in GPe and GPi. Nambu et al. (2000) showed that blockade of NMDA receptors (but not that of non-NMDA glutamate receptors) in STN attenuated early and late excitatory responses to cortical stimulation in both GPe and GPi. Muscimol delivered into STN, which blocked all activity there, also abolished early and late excitation in both GPe and GPi. Spontaneous activity (in the waking state) was reduced by 0–78% in both GPe and GPi. Other similar correlational evidence involves changes after dopamine denervation. To explain it, we must first consider direct effects of dopamine on the subthalamus.

3.4.2 Dopamine in the Subthalamic Nucleus, and Changes in Neural Activity There, after Dopamine Denervation

It is widely accepted that Parkinson's disease arises largely or entirely from degeneration of dopaminergic axons innervating the basal ganglia. The general belief is that denervation of the dopamine supply to the striatum (specifically the putamen, according to Kish et al., 1988) is sufficient to produce the symptoms of the disease. It might, therefore, be thought that the classic motor symptoms of Parkinson's disease could be explained in terms of dynamic changes occurring primarily in the striatum, when the putamen is severely depleted of its dopamine. As discussed below (Section 3.4.5), many striatal neurons undergo an increase in firing rate in association with parkinsonian states. It is also known that firing rate of neurons in the STN is markedly elevated in animal models of Parkinson's disease (see, e.g., Miller and DeLong, 1987; Bergman et al., 1994; Kreiss et al., 1997; Magill et al., 2001; but also see Ni et al., 2001). This fact has been attributed to the increase in firing rate in striatal neurons leading to disinhibition via GPe (the conventional "indirect" pathway). However, it needs to be asked whether the effects of dopamine denervation on firing in STN are exerted indirectly via such links from the striatum or more directly by dopamine denervation in STN itself. A growing body of evidence suggests that the latter as well as the former is the case.

The striatum is not the only part of the basal ganglia with a significant dopamine innervation. For instance, GPi is known to have a dopamine innervation (Parent and Smith, 1987; Lavoie et al., 1989). It has also been recognized for some time that STN has a dopaminergic innervation in rats (Brown et al., 1979; Campbell et al., 1985; Cragg et al., 2004). In tissue punches of rat STN, dopamine increased cAMP production (Brown et al., 1979), which suggests that dopamine acts there in part via D1 receptors. In addition, a recent study of Murer et al. (1999) showed that STN in rats contains D2 receptors, which proliferate after 6-hydroxydopamine (6-HD) lesions (indicating that these are not autoreceptors). STN of cats also contains a dopaminergic innervation (Meibach and Katzman, 1979; Rinvik et al., 1979). Until recently, it has been unclear whether there was a dopaminergic innervation of STN in primates. Such an innervation had been reported in cynomolgus monkeys

(Rinvik et al., 1979), but in squirrel monkeys (according to Lavoie et al., 1989) only a small part of STN had such an innervation. However, Cossette et al. (1999) demonstrated tyrosine hydroxylase-positive fine axons innervating pallidum and STN in humans, these being collaterals of nigrostriatal axons. François et al. (2000) detected the same projection in vervet (African green) monkeys by tyrosine hydroxylase staining, as well as by retrograde and anterograde tracing. The tyrosine hydroxylase-positive axons were reduced by 51% in monkeys treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), and by 65% in monkeys treated with parkinsonian humans. Augood et al. (2000) could detect no D1- or D2-RNA-positive cells in the human STN (although these were seen in striatum). A weak D1-like receptor binding was seen in STN. They suggested that there were presynaptic D1 receptors in STN.

The mode of action of dopamine in STN is unresolved as it still is in the striatum. Dopamine has been shown to have excitatory effects (Mintz et al., 1986) apparently due to activation of D1 rather than D2 receptors (Kreiss et al., 1996), and Cragg et al. (2004) found that dopamine application depolarized STN neurons. However, Campbell et al. (1985), and Hassani and Féger (1999) found that dopamine delivered iontophoretically or by microinfusion suppressed STN neuronal discharge in normal rats, again apparently via D1 receptors. Moreover, as just mentioned, firing rate of neurons in the STN is elevated in animal models of Parkinson's disease. Hassani et al. (1996) provided evidence against this being due to disinhibition consequent on increased striatal activity via GPe (pallidum in rats). They found that destruction of the pallidum in rats led to only slight elevation in the firing of STN neurons, whereas 6-HD lesions producing a parkinsonian syndrome led to an average increase in firing by more than 100%. Similar results were obtained by Magill et al. (2001): In rats, dopamine depletion using 6-HD led to a large increase in firing rate in STN neurons (233% of control), although there was no significant change in firing rate in the pallidum. In a related study of Stefani et al. (2002), human parkinsonian patients at operation received systemic doses of apomorphine, which remedied the hypokinesia. This did not modify significantly the firing frequency of GPe cells, but with the same doses STN cells showed a reduction in firing frequency, and GPi cells also underwent a reduction in firing frequency. These results have led to the suggestion that the symptom picture of Parkinson's disease cannot be understood just on the basis of dopamine deficit in the striatum, and that dopamine has important direct actions in other structures of the basal ganglia, notably in STN (for further discussion, see Chapter 8).

Although details of the actions of dopamine and its receptor subtypes in STN are unresolved, it is clear that after dopamine denervation in animals and in human parkinsonian syndromes, firing of STN neurons increases, and this is probably directly due to loss of an inhibitory dopaminergic effect in STN. An indirect effect, due to dopamine loss in the striatum, increased input to GPe from the striatum, and reduced inhibition of STN from GPe, contributes little, if anything, to the change in STN firing. Further support for this conclusion comes from Ni et al. (2000). In rats, they found that 6-HD lesions of substantia nigra pars compacta (SNC) produced a large increase in the proportion of neurons with burst firing in GPe. When STN lesions were combined with the SNC lesions the firing pattern returned to that of normal rats, that is, burst firing disappeared. The change in firing in GPe thus appeared to be

dependent on changes in STN, rather than in the striatum. This conclusion supports that discussed in the previous subsection, that STN has a major excitatory influence on GPe. There is less evidence that GPe exerts inhibitory control over STN, although this interaction may sometimes apply.

3.4.3 Evidence that Neural Activity in GPe and GPi Have Opposite Signs of Relation to Behavior

In the paragraphs below, evidence is reviewed suggesting that neural activity in GPe, GPi, and SNR is related to the overall level of active behavior, and that neural activity in GPi and SNR has a relation to behavioral output of opposite sign compared with that in GPe. The emphasis is on relations to overt behavior because this is observable; but similar relations are implicit for the internalized processes (attentional focus, motivational target) dealt with by other functional circuits through the basal ganglia. Electrophysiological evidence in single-unit studies is given greatest emphasis because it is most direct. Evidence is considered step-by-step, working back from GPi and SNR, via GPe to the striatum. Evidence on neural activity in GPi is the least ambiguous and is dealt with first. Evidence on GPe is in line with the usual concept of the "indirect" pathway, but in some respects still leaves the exact specification of the indirect pathway uncertain. As mentioned above, it is often assumed that GPe projects indirectly to GPi and SNR via STN. However, as just discussed, most of the evidence indicates that this potential route is employed little or not at all. An alternative explanation of the oppositional role of GPe and GPi/SNR can easily be provided by the fact that GPe sends potent inhibitory projections direct to these output nuclei (Figure 3.1A).

The evidence that points most clearly to a definite functional division between direct and indirect pathways is electrophysiological data obtained from human subjects with disorders of the basal ganglia, or (more commonly) animals with induced models of these disorders. The disorders in question are Parkinson's disease and Huntington's disease. Both of these have very complex motor phenomenology (discussed in more detail in Chapters 7 and 8). Here, we are concerned with overall levels of motor activity. One of the most prominent symptoms of parkinsonism is known as bradykinesia or akinesia—a reduction in overall levels of motor activity—while a prominent aspect of Huntington's disease is "hyperkinetic," the symptoms of chorea, athetosis, and ballismus. Abnormal involuntary movements (dyskinesia), sometimes appearing in parkinsonian syndromes during L-DOPA therapy, is another hyperkinetic syndrome.

3.4.3.1 Relation Between Levels of Motor Activity and Neural Activity in GPi or SNR

From the analysis of the sign and target of projections in the basal ganglia presented above, one would expect that in hypokinetic disorders, such as parkinsonian akinesia or bradykinesia, there would be an increase in the firing rate in neurons of the basal ganglia, which directly control neurons in the motor thalamus, that is, those of the output nuclei (GPi and SNR). In contrast, in hyperkinetic syndromes,

neurons in GPi and SNR should undergo reductions in firing rate. Parkinsonian akinesia can be produced reliably in experimental primates with the toxin MPTP and a similar syndrome can be produced in rats using the toxin 6-HD (usually given unilaterally), both of which destroy the midbrain dopamine neurons. In MPTP-lesioned monkeys, Miller and DeLong (1987) found that, after the lesion, during periods of stable parkinsonian akinesia before recovery set in, neuronal discharge rates increased in GPi (from a mean of 79.5 Hz in untreated animals to 100.8 Hz [$p < 0.001$]). Similar results were obtained by Filion and Tremblay (1991), who stress that the demonstration of such effects depended on near-complete dopamine denervation and avoidance of delays when symptomatic recovery might have occurred. The increase in firing rate in GPi correlated with manifest akinesia. The authors also reanalyzed data from an earlier study (Filion, 1979) to show that an acute electrolytic lesion of the midbrain dopamine neurons (in SNC) also raised the firing rate in GPi. Other confirmations of these findings are by Boraud et al. (1998) and Heimer et al. (2002), although in the latter study the increase did not reach statistical significance. In rat models of parkinsonism, SNR neuronal discharge rates have also been found to be elevated (Burbaud et al., 1995; Chang et al., 2003).

Several studies fail to replicate the result: Wichmann et al. (1999) found no significant change in mean firing rate in either GPi or SNR, after MPTP treatment had produced severe parkinsonian symptoms. Raz et al. (2000) report that firing rates in GPi in two MPTP-treated monkeys were nonsignificantly decreased (down by 11% in the first monkey at 5 days after MPTP administration and by 20% in the second at 3 days after administration). Both monkeys were quite akinetic even towards the end of the study period. Four studies of SNR unit firing in rats found that dopamine depletion led to a *decrease* in firing rate (MacLeod et al., 1990; Rohlfs et al., 1997; Tseng et al., 2001b) or no significant change (Sanderson et al., 1986). In another study in rats, there was no difference in firing rate of EP neurons between controls and dopamine-depleted animals (Ruskin et al., 2002). How can these discrepancies be explained? The studies in rats are not critical tests of the behavioral role of unit firing in basal ganglia output nuclei, since they were conducted in anesthetized animals, or, in the study of Ruskin et al., in immobilized animals.* However, this cannot explain the discrepant results in the two studies in monkeys.

Electrophysiological evidence concerning predicted changes in unit firing rates in the output nuclei in association with hyperkinetic syndromes is provided by several papers. Some of these are studies of models of hyperkinetic syndromes in experimental primates, rather than of naturally occurring chorea–athetosis or ballism in Huntington's disease, or Parkinson's disease treated with L-DOPA. In the study of Filion et al. (1991), monkeys were made parkinsonian by administering MPTP. Then, short-lived periods of dyskinesia were produced by systemic injection of the dopamine agonist apomorphine. In these hyperkinetic periods, firing rates

* An early study with relevant data is that of Iansek (1980). In free-to-move monkeys, administration of reserpine produced akinesia, which was accompanied by marked reduction in the rate of discharge of neurons in GP. Indeed, many of the neurons became electrically silent, and could be detected only by their injury discharge. Although both segments of GP were recorded from in Iansek's experiments, the paper does not specify whether this particular finding applied to GPe, GPi, or both.

in 90% of the recorded GPi neurons were reduced, sometimes almost to zero. This result has been confirmed in parkinsonian monkeys by Papa et al. (1999) using L-DOPA and by Boraud et al. (2001) using apomorphine or piribedil (but not the D1 agonist SKF38393). Hutchinson et al. (1997b), Merello et al. (1999), and Lozano et al. (2000) obtained the same result in humans awaiting surgery, using apomorphine, especially if the drug caused dyskinesia. Levy et al. (2001) found in humans that apomorphine led to a fall in firing rate in GPi neurons during the "on-state" even when dyskinesia was absent. Ruskin et al. (2002) used a rat model of hyperkinetic disorder, in which unilateral dopamine-depleted animals are challenged with dopamine agonists resulting in typical rotatory locomotion. Dopamine D1 agonist treatment or combined D1/D2 agonist treatment inhibited firing of neurons in EP.

Further evidence from normal freely moving rats was reported by Gulley et al. (1999). While exploring an open field, unit firing in the majority of SNR neurons (79%) showed increases in firing rate, and the remainder showed decreases. Systemic injection of amphetamine, which produced locomotor hyperactivity and rearing, strongly inhibited the firing of most units, and this could be reversed by a subsequent injection of the D2 dopamine blocker, haloperidol, in association with a reduction of locomotor activity.

This evidence is mainly consistent with the oppositional control of neurons in GPi in relation to hypo- versus hyperkinetic syndromes. There is, however, some discrepant evidence for the hypokinetic syndromes. A possible explanation is that, in parkinsonian syndromes, units in GPi (as in GPe) often show high-frequency burst firing (see Section 8.6). Whereas the maintained level of tonic activity in these nuclei is probably an accurate reflection of the concurrent sustained level of depolarization, when burst firing occurs it is a sign of a brief (though repeated) episode, which interrupts the tonic firing, and is likely to have a more complex relation to membrane potential. How such burst firing influences overall discharge frequency is difficult to determine. High-frequency burst firing would tend to increase overall impulse frequency, but periods of silence in the phase of recovery after each burst might lower the mean frequency (see, for instance, Filion and Tremblay, 1991, Figure 2B; Burbaud et al., 1995, Figure 7B; Ni et al., 2000, Figure 1C). Burst firing may thus either exaggerate or diminish the firing rate as determined by membrane potential. For instance in GPe, during a parkinsonian state, mean unit firing rate is reduced or unchanged, but the mode of interspike intervals is reduced, a measure of the superimposed burst firing (Filion and Tremblay, 1991; Ni et al., 2000). Unless burst firing is absent, the mean firing frequency is not an absolute guide to the balance of synaptic influences on neurons in these nuclei. It *is* a relevant measure, but not one that can bear the full burden of proof of the role of the direct versus indirect pathways in parkinsonian state. However, other types of evidence, such as that coming from microinjection of drugs, provide supplementary support for conclusions based on firing frequency.

Several micropharmacological experiments support the conclusion derived from most of the electrophysiological data. According to Scheel-Krüger et al. (1981), injection of the GABA antagonist picrotoxin into either EP or SNR in rats caused behavioral sedation and mild catalepsy (a form of whole-body rigidity commonly studied in rodents, thought to be equivalent to parkinsonian rigidity in humans). In the study

of Matsui and Kamioka (1978), injection of a GABA agonist into SNR in rats led to a period of motor hyperactivity. Similar results were obtained by Scheel-Krüger et al. (1981), who describe the effects of muscimol injection into either SNR or EP as similar to those produced by systemically administered dopamine agonists, including locomotor hyperactivity, followed by focused stereotyped behavior (sniffing, licking, and gnawing). (There were some differences in detail between the effects produced in SNR and EP.) Similar relations between neural and motor activity levels were shown by Robertson et al. (1989), who produced choreic or ballismic dyskinesia in primates following injection of an excitatory amino acid antagonist, kynurenate, into GPi.

There are, in principle, several possible causes of increased firing in GPi (in hypokinetic syndromes) and reduced firing there (in hyperkinetic syndromes). If we adopt the conventional view of the "indirect" pathway, activity in STN drives activity in GPi. These syndromes would then be produced, respectively, by increases and decreases in neural activity in STN. There is some evidence compatible with this: Biggs et al. (1997) measured release of the excitatory amino acids aspartate and glutamate in the EP of rats using microdialysis probes. A D2 antagonist, delivered intraperitoneally in a dose sufficient to produce catalepsy, increased the release of these substances. The same effect was seen when catalepsy was produced by dopamine denervation with 6-HD or by reserpine pretreatment. In reserpine-pretreated rats, the D2 agonist, quinpirole reduced release of these amino acids to normal levels. A D1 antagonist SCH23390 had no effect and the D1 agonist SKF38393 was also inactive. The results were taken as indicating that the excitatory control of EP by STN, supposedly part of the indirect pathway, is under the influence of striatal D2 but not D1 receptors. That the point at which the D2 antagonist was acting was the striatum, rather than elsewhere, was supported by the fact that a D2 antagonist had the same effect when delivered intrastriatally in anesthetized animals.

However, these results are nonspecific evidence for the role of the indirect pathway from striatum via GPe to STN. Catalepsy is a major behavioral disturbance, and may be accompanied by changes in the cortical input to the STN, rather than changes in the striatal pathways via GPe to STN. 6-HD lesions on one side produced significant increases in amino acid output on both sides, suggesting that indirect effects, as well as those mediated by pathways through the basal ganglia are important. Moreover, there were unexplained inconsistencies in these experiments: While the D2 antagonist haloperidol produced increased release of amino acids, another D2 antagonist, raclopride, did not. The D2/D3 agonist RU 24213 reversed reserpine-induced akinesia, but, unlike quinpirole, paradoxically increased glutamate release in EP. Given these caveats, direct effects of dopamine depletion or blockade in STN could explain the results of Biggs et al. (1997). This is supported by two studies: Parry et al. (1994) showed that apomorphine microinfusion into STN caused oral dyskinesia in rats, blocked by D1 antagonists (given systemically or by coinfusion) but not by D2 antagonists. Mukhida et al. (2001) showed in 6-HD parkinsonian rats that transplants of dopaminergic cells at multiple sites (including STN) led to more complete recovery of function than just striatal transplants.

The direct pathway from striatum to GPi/SNR was not mentioned in the above paragraphs. According to one view, striatal dopamine has opposite actions on neurons of origin of the direct and indirect pathway. According to this view, in

low-dopamine (parkinsonian) states, there is elevation of firing in the neurons of the indirect pathway and a reduction in firing in those of the direct pathway. Because the two pathways have different numbers of inhibitory links, their respective actions on neurons of GPi/SNR would then be synergistic. However, the supposed oppositional role of dopamine on the two classes of striatal projection neurons is, to say the least, debatable (see Section 3.4.4). Moreover, there is no direct evidence for reduction in firing of striatal neurons of the direct pathway in low-dopamine states. A more broadly based discussion of the control of GPi unit firing is delayed until Section 3.4.5. This leads to the suggestion that firing in *both* classes of striatal projection neurons may be elevated in low-dopamine states, and that the elevated firing in those of the direct pathway then sometimes leads to *hyper*kinetic syndromes in these states.

3.4.3.2 Relation Between Levels of Motor Activity and Neural Activity in GPe

The evidence just considered shows that activity in STN, under either excitatory control from the cortex or inhibitory control from dopaminergic input can drive GPi neurons and determine levels of motor activity. However, evidence on the input and output connectivity of GPe, and the sign of the various links, suggests that neuronal firing in GPe should have a relation to motor activity levels the opposite of that in GPi or SNR. This leads one to expect that in GPe there would be a decrease in firing rate in hypokinetic syndromes and an increase in hyperkinetic ones. Since GPe neurons give inhibitory inputs to GPi, the changes in firing in GPe could then be part of the explanation of the changes observed in GPi. Substantial evidence supports these possibilities.

In accord with these predictions, in the study of Miller and DeLong (1987) mean firing rate for GPe neurons fell, after MPTP administration (from a mean of 66.7 to 46.2 Hz [$p < 0.001$]). Similar results were reported in monkeys by Filion and Tremblay (1991), Boraud et al. (1998), and Heimer et al. (2002). Raz et al. (2000) found, in one monkey, that 5 days after an MPTP lesion, mean firing rate in GPe neurons had fallen by 23% ($p < 0.07$), and in another, studied 3 days after the lesion, the reduction was 33% ($p < 0.01$). In the study of rats by Pan and Walters (1988), mean pallidal firing rate fell after 6-HD administration from 40.6 $\pm$ 2.3 to 31.9 $\pm$ 4.1 at 1 week after the lesion, a reduction which was maintained until 6–9 weeks after administering the toxin.

Two studies have failed to find a decrease in GPe firing rate in parkinsonian animals: In that of Montgomery et al. (1985), no proper control condition was reported, norms for GPe firing rate being taken from other published papers and there was no report of the correlation with actual akinesia. In the other paper (Hassani et al., 1996), a nonsignificant 14.6% decrease in firing rate was reported. However, the electrophysiological analysis was carried out on urethane-anesthetized rats, which, according to Pan and Walters (1988) eliminates the difference between parkinsonian and intact animals.

In hyperkinetic syndromes the predicted increase in firing in GPe has also been confirmed. Filion et al. (1991) reported that, during the short-lived periods

of dyskinesia produced by apomorphine injection after MPTP, firing in 87% of GPe neurons increased by 15–270%. Boraud et al. (2001) confirmed this result in monkeys, as did Hutchinson et al. (1997b) and Lozano et al. (2000) in human Parkinson's disease patients awaiting surgery and treated with dopamine agonists. Boraud et al. (1998) found only nonsignificant increases in GPe unit firing rate after L-DOPA, but variance used in the two monkeys was very large despite the presence of classic clinical effects.

Micropharmacological experiments produce results supporting the predicted relation of motor activity levels to neural activity in GPe. Several studies have shown that microinjection of a GABA agonist into the rat pallidum produces catalepsy and rigidity (Matsui and Kamioka, 1978; Moroni et al., 1978; Scheel-Krüger et al., 1980, 1981; Scheel-Krüger, 1983). In some cases (Turski et al., 1984; Ellenbroek et al., 1986), catalepsy is produced by such injections into the ventral striatum. The ventral striatum is cytologically similar to the dorsal striatum, and normally, its neurons have a low level of firing, which cannot be lowered much further by the presence of a GABA agonist. The balance of evidence suggests that the effects here are produced from spread of the injected drug to the immediately adjacent pallidum that has much higher levels of tonic activity susceptible to drug-mediated reduction. Thus, Scheel-Krüger (1983) finds that, for ventral striatal injections, catalepsy can be produced only for injections within ~0.5 mm of the pallidum, and the intensity of the catalepsy and the speed of its onset is related to the distance from the neighboring ventral pallidum. That such an effect is produced by disinhibition of the basal ganglia output nuclei is shown by the fact that it is abolished if, simultaneously, a GABA agonist is injected into SNR (Turski et al., 1984).

Four experiments in primates, using microinjections of a GABA antagonist bicuculline into GPe, also support the prediction (Crossman et al., 1988; Mitchell et al., 1989; Matsumura et al., 1995; Grabli et al., 2004), these injections producing a hyperkinetic movement disorder. A similar effect had earlier been demonstrated (Crossman et al., 1984, 1988) with injection of bicuculline into certain parts of the striatum, but since these were confined to injections in the parts nearest to GPe, the result may have been due to spread of the injected drug. Presumably, these results arise because GPe neurons are no longer prevented from inhibiting the output nuclei, so that the neurons of the motor thalamus are in turn released from inhibition. Matsumura et al. (1995) also produced short-lived periods of dyskinesia in normal monkeys by microinjection of bicuculline into GPe, while recording from units in both GPe and GPi. The results were more complicated than in the above two studies: In GPi, 56% of units showed a reduction in firing, either initially (41%) or after an initial increase in firing rate (14%). However, an even larger proportion showed an increase in firing rate (85%) either initially (59%) or after an initial decrease (26%). In GPe, 85% of neurons showed an increase, 14% of which also showed an initial decrease and 14% showed a decrease without subsequent increase. These results give equivocal support to the predicted changes in unit firing associated with hyperkinetic symptoms. However, the authors suggest that in GPe, the primary effect *is* disinhibition (i.e., increased firing), but this has transsynaptic effects within GPe, via the recurrent inhibitory collaterals of the activated cells, which lead to decrease of activity in other neighboring cells. Such effects of opposite signs in GPe would

in turn be likely to produce converse effects in GPi—again combining responses of opposite signs. Thus, the results of Matsumura et al. (1995) are not incompatible with those of the other two studies.

Two studies have been reported in rats where the GABA antagonist picrotoxin was microinjected into the pallidum (=GPe). Scheel-Krüger (1983) reported that this had no, or at most a modest effect in stimulating behavior, although similar injections into the adjacent part of the striatum produced vigorous locomotion and rearing. In contrast, Ossowska et al. (1984) found that injection of picrotoxin into the pallidum produced marked locomotor stimulation, a result consistent with those obtained in primates. Such experiments may be more reliable in animals with larger brains, where spread of injected drugs to neighboring structures is less of a problem.

A result seemingly contradicting the supposed role of increased neural activity in GPe in hyperkinetic syndromes is that of Blanchet et al. (1994). They showed that dyskinesia produced in MPTP-treated monkeys by administration of L-DOPA was not relieved by axon-sparing lesions of GPe. However, in three of the four monkeys used, the lesion was not complete, and in the single monkey where it was complete, dyskinesia could not be produced by L-DOPA treatment. Completeness of the lesion of GPe may be critical, if (as argued in Section 4.4) pathways through this nucleus are used wherever they can be found without limitations set by neighborhood relations typical of somatotopically organized projections.

Assessment of levels of neural activity in nuclei of the basal ganglia has sometimes been based on metabolic markers (such as 2-deoxyglucose) rather than electrophysiological measures. Interpretation of results with these markers is difficult, because it is not clear whether increase in metabolism reflects excitatory or inhibitory processes, and the balance between pre- and postsynaptic metabolic activity is unclear. One of the more specific metabolic markers is the enzyme cytochrome oxidase, whose activity is dependent on mitochondrial oxidative metabolism. This has been used to show that GPe does not undergo reduced activity in parkinsonian syndromes (Vila et al., 1997), an apparent contradiction to the above evidence. However, even this marker reflects, to some degree, pre- as well as postsynaptic activity, especially in inhibitory terminals (Carroll and Wong-Riley, 1984; Kageyama and Wong-Riley, 1985). In parkinsonian syndromes, reduced postsynaptic neural activity in GPe may be combined with increased presynaptic activity. The absence of change in oxidative metabolism is thus an uncertain way of determining neural activity of GPe neurons.

3.4.3.3 Relation Between Striatal Neurons of Origin of Direct and Indirect Pathways, and Levels of Motor Activity

What could be the cause of the changes in firing rate in GPe and GPi in hypo- and hyperkinetic movement disorders? To explain the decreased firing rate in GPe (in hypokinetic states) and increased firing there (in hyperkinetic ones), one might envisage an excess of activity in striatal inhibitory axons targeting GPe (for hypokinetic states) and a deficit of activity in such axons (for hyperkinetic ones). To explain the changes in GPi, one might envisage converse changes in the striatum (deficient striatal activity in hypokinetic states, an excess of activity in hyperkinetic ones).

These alternatives are of course incompatible, but might apply to different classes of striatal neurons, the origin, respectively, of the indirect and direct pathways. A third possible dichotomy of functional relations is that hypokinetic states might arise from excess activity in neurons of origin of the indirect pathway, leading to neural activity being reduced in GPe and increased in GPi or SNR; while hyperkinetic states might arise from excess activity in neurons of origin of the direct pathway, or activity in such neurons unopposed by that in the indirect pathway, leading to reduced neural activity in GPi or SNR. This last dichotomy has more instrinsic appeal, because it gives a rationale for there being separate direct and indirect pathways with opposite signs of relation to activity levels (whereas they become synergistic for the first two proposals). It is discussed below, mainly in relation to neuropathological findings about Huntington's disease.

None of these alternatives implicates the subthalamus. The reduction of neural activity in the output nuclei associated with hyperkinetic states (e.g., in Parkinson's disease, after treatment with dopamine agonists) need not be a consequence of reduced excitatory drive from the subthalamus, since, according to Levy et al. (2001), firing rate of STN neurons was unchanged by apomorphine, under conditions where GPi neuronal firing rate fell. A further complication to these relationships is that dopamine might act in different ways, and via different dopamine receptors on the striatal neurons of origin of the direct versus the indirect pathways. This is discussed later (Section 3.4.4).

In terms of symptoms, Huntington's disease is characterized by "hyperkinetic" phases with abnormal excessive movements ("chorea," "athetosis," and "ballismus,"—see introduction to 3.4.3), but there are other stages to the disorder, which are hypokinetic, characterized by akinesia and rigidity, with inability to produce voluntary movement. Sometimes, the hyperkinetic phase occurs early in the course of the disease, the hypokinetic phase taking over in the later stages. Juvenile-onset cases are often dominated by hypokinesia and rigidity from the start (Bruyn, 1968). In terms of neuropathology, Huntington's disease is overall a degenerative condition, with cell loss confined mainly to the medium-sized spiny cells of the striatum (Bruyn, 1968). However, in animal models, it has been quite impossible to replicate the hyperkinetic phase of the disorder by striatal lesions (see review of the behavioral effects of striatal lesion in Section 4.5).

A possible explanation of this apparent paradox, based on the distinction between direct and indirect pathways, comes from neuropathological study of early and late stages of this disorder. Since striatal cells of origin of the direct and indirect pathways can mainly be distinguished by their different peptide content (see Section 3.2), useful methods are provided for further analysis of their respective roles in human neuropathology. Initial studies had shown no differential loss of ENK versus SP (Emson et al., 1980; Marshall et al., 1983), or a loss which did not differentiate between direct and indirect pathway nuclei (Seizinger et al., 1986). However, later study made a more interesting discovery (Dawbarn et al., 1986; Reiner et al., 1988; see also Albin et al., 1990) using immunocytochemical techniques to assess the levels of the different peptides in GPe and GPi, derived respectively from striatal projections of the indirect and direct pathways. It was shown that, in the choreic stages of the disease, content of ENK in GPe was markedly reduced and was much more severely

affected than the SP content of GPi. In the more severe rigid akinetic stages of the disease, all striatal target areas were depleted of their respective peptidergic projections. The greater vulnerability in low-grade Huntington's disease of the ENK striatal projection than the SP projection has been confirmed both in established cases (Sapp et al., 1995; see also Ferrante et al., 1990) and in two presymptomatic cases (Albin et al., 1992). Storey and Beal (1993), however, did not confirm the differential loss in choreic cases of Huntington's disease. In addition to the studies of peptides in the terminal fields, it has also been shown that there is preferential loss of cells in the striatum reacting for ENK, compared with those reacting for markers of SP, in both early and later stages of Huntington's disease (Richfield et al., 1995), although this differential loss was not confirmed in one study (Augood et al., 1996).

A further indication that in Huntington's disease the striatal projection to GPe is more vulnerable than that to GPi is that there is more severe loss of GABA in GPe than in GPi (Spokes, 1980; Spokes et al., 1980; Reynolds and Person, 1990; Pearson et al., 1990; Storey and Beal, 1993), especially in the early stages of the disease. In the study of Pearson et al. (1990), the GABA loss in both regions was more severe in the "mild chorea" group of cases (5/7 of which showed rigidity) than in the "severe chorea" cases* (0/11 of which showed rigidity, but showed prominent chorea). A similar conclusion can be drawn from the study of Richfield and Herkenham (1994) showing that cannabinoid receptors (known to be a marker of striatal projections) are lost to a greater degree in GPe than in GPi in Huntington's disease.

The implication of this fairly robust body of evidence is that the cells of origin of the indirect pathway from the striatum are lost differentially in Huntington's disease, compared with those of the direct pathway. Since the former influence the cells of the motor thalamus with three reversals of sign (a net inhibitory influence), while the latter influence them with two reversals (a net excitatory influence), one has a plausible explanation for the fact that "mild" or early stages of the disease exhibit a hyperkinetic symptomatic picture. The fact that neither hyper- nor hypokinetic symptoms are seen in animal models with lesions of the striatum is then explained by noting that such lesions would not differentially affect neurons of origin of the direct versus the indirect pathway, given that the two types of neuron are closely intermingled (see Section 3.2).

In principle, the role of GPe and the indirect pathway could also be investigated in animals, if it were possible selectively to destroy striatal neurons of origin of this pathway. A recent paper (Sano et al., 2003) has devised a method of doing this. Using an immunotoxin specific for the dopamine D2 receptors, it was possible to make selective striatal lesions in mice, which destroyed almost all D2 receptor-containing neurons, but left D1 receptor-containing neurons intact. The contentious evidence, which correlates such receptor content respectively with the neurons of origin of the indirect and direct pathways, is considered in Section 3.4.4. However, in terms of the neuropeptide markers considered above, this lesion also led to a loss of 91% of

* The terms "mild" and "severe" appear to be used in a different sense from that in the foregoing paragraphs. The actual symptoms mentioned are more relevant to the argument here than how they are referred to.

ENK-containing neurons, but left intact those with SP precursor peptides. Therefore, it is likely that the neurons of origin of the indirect pathway were destroyed sparing those of origin of the direct pathway. Behavioral studies of these mice revealed interesting anomalies. When normal rodents are challenged with a dose of amphetamine, locomotor hyperactivity is seen, and if the animals have been treated so that the striata on the two sides are asymmetrically depleted of dopamine, the locomotion of the animals is asymmetric, turning away from the striatum with highest dopamine activity (Miller and Beninger, 1991). The exact reasons for this asymmetry of behavior are complex, reflecting the fact that the striatum contains a variety of loci, each part of different functional circuits (Miller and Beninger, 1991). In the mice, in the experiments of Sano et al. (2003), amphetamine led to less hyperactivity than in normal mice and to circling ipsilateral to the lesioned side (i.e., contralateral to the side with greatest dopamine activity). These facts do not depart from those obtained with nonselective dopamine receptor elimination (see Giorgio and Biggio, 1990). However, the spontaneous behavior of the mice was more interesting. They had higher-than-normal levels of spontaneous locomotion and this locomotion led them to circle contralateral to the lesion, that is, toward the side where the striatum had highest dopamine activity. These are effects contrary to the usual hypoactivity and contrary to the direction of circling in unilaterally dopamine-depleted rodents. The results can however be explained if the lesion is specific to neurons whose activity leads to behavioral suppression, that is, hypothetically, those of origin of the indirect pathway. This experiment therefore provides supporting behavioral evidence for the proposed role of the indirect pathway.

3.4.3.4 Summary

Overall, the evidence presents a complex picture of interactions among the striatum, STN, GPe, and GPi. In pathological conditions (Huntington's disease and parkinsonian akinesia or dyskinesia), neural activity in GPe and GPi undergoes changes in opposite directions, this being reflected in overall levels of motor/behavioral activity. Thus, increases in firing rate occur in GPi in association with hypokinetic syndromes and in GPe in association with hyperkinetic ones; and decreases in firing rate occur in GPi in association with hyperkinetic syndromes and in GPe in association with hypokinetic ones. Some experiments show that STN is under tonic restraint from GPe, but it is not clear that this is an essential link in the indirect pathway to the output nuclei. In contrast, electrophysiological experiments clearly show control from cortex to STN to GPe. In some experimental circumstances involving change in STN, activity in GPe and GPi changes in parallel. Thus, while there is some evidence that GPe exerts inhibitory control over STN, the evidence is more abundant that STN has a major excitatory influence on GPe, suggesting that it is best seen as an input nucleus of the basal ganglia. The two influences are apparently in opposition to each other. However, the role of the two processes may be clarified by the suggestion that excitatory control via STN is driven by activity from cortex, while inhibitory control of STN from GPe is a reflection of tonic activity in GPe, which can change to disinhibition if the cortex also activates the inhibitory striatal projection neurons.

3.4.4 Supposed Separate Cellular Locations and Actions of Different Dopamine Receptors on Neurons of Origin of the "Direct" and "Indirect" Pathways

Another body of evidence has been held to support distinct roles for the direct and indirect pathways from the striatum. It is related to the cellular location—and actions mediated by—different dopamine receptors. This evidence is complex, involving cytology and histology, as well as functional studies based on biochemical, electrophysiological, and behavioral measures. As far as function goes, this evidence has led to the widespread acceptance of the view that dopamine has opposite signs of action via D2 receptors on striatal neurons of the indirect pathway and via D1 receptors on those of the direct pathway. Such ideas have been proposed by Gerfen et al. (1990, 1991), who concludes, "dopamine appears to oppositely affect the function of the two major output pathways of the striatum, which regulate the activity through the basal ganglia" (Gerfen, 2000). Likewise, Albin et al. (1989) in a widely cited paper write "the differential effect of dopamine on different subpopulations of striatal projection neurons suggests that differential regulation of striatal projection neuron subpopulations by striatal afferents may be an important feature of striatal function." This idea was proposed in part because it explains the opposite directions of firing rate change in GPe versus GPi in hyper- and hypokinetic disorders, both nuclei receiving inhibitory projections from the striatum. However, there are clearly other possible explanations of these findings, since GPe as well as the striatum exerts inhibitory control over GPi. Whatever the truth of this, these opposite changes in firing rates are closely related to the excesses and deficits in levels of motor activity. So it is clear (in the account of Albin et al.) that D1 versus D2 receptors in the striatum are envisaged to have opposite signs of action with effects not just local to the striatum, but expressed in terms of motor activity levels. For the sake of simplicity, this interpretation is referred to below as the "Gerfen/Albin hypothesis." The evidence contains major disagreements, the resolution of which is theoretically important, if only to refute well-established beliefs.

3.4.4.1 Cytological and Histological Studies

As mentioned above, dopamine receptors are of several types (D1, D2, D3, D4, and D5) and subtypes, but broadly they can be divided into two classes—D1-like (including D1 and D5) and D2-like (including D2, D3, and D4) (Civelli et al., 1993; Sibley et al., 1993). Activation of D1-like receptors increases the production of cyclic AMP (cAMP) in the striatum, while activation of D2-like receptors has either no effect or decreases cAMP production. As described above, the majority of striatopallidal neurons express the peptide ENK. Neurons identified as containing ENK have also been found to express the D2 dopamine receptor messenger RNA (mRNA) (Le Moine et al., 1990, 1991; Gerfen et al., 1990). In contrast, striatonigral neurons express the peptides SP and DYN, and neurons in which these neuropeptides are found also express the D1 dopamine receptor mRNA (Gerfen et al., 1990). These findings were supported by Le Moine and Bloch (1995), who provide more quantitative data. Using highly sensitive complementary RNA (cRNA) probes, applied to analysis of several

thousand neurons in the striatum and nucleus accumbens, it was found that ~96% of ENK-positive neurons colocalized mRNA for D2 receptors, ~98% of SP-positive neurons colocalized D1 receptors, but only ~4% of ENK-positive neurons colocalized mRNA for D1 receptors, and only ~4% of SP-positive neurons colocalized mRNA for D2 receptors. Further support for covariation of peptide and dopamine receptor content of striatal neurons is provided in the paper of Sano et al. (2003) mentioned above: A selective lesion produced with an immunotoxin specific for D2 receptor-containing cells also led to a loss of 91% of ENK-positive cells, while those positive for the SP precursor peptides were unaffected.

Other studies present a more complex picture. Lester et al. (1993), using labels specific to receptor mRNAs, showed that mRNA for either D1 or D2 receptors was present in about 65% of striatal neurons, and of these, about 27% colocalized both mRNAs. Surmeier (2000; see also Surmeier et al., 1996a) carried out single-cell studies using reverse transcriptase polymerase chain reaction (RT-PCR). In confirmation of previous studies, dopamine receptor mRNA expression was strongly correlated with the expression of peptide mRNAs. All SP-positive neurons (~40% of the total) expressed high levels of D1 mRNA and ~19% of these also expressed D2 receptor mRNA. All ENK-positive neurons (~40% of the total) expressed high levels of D2 mRNA (both short and long isoforms) and ~11% of these expressed D1 mRNA. Neurons that colocalized these peptides (~20% of the total) also colocalized both D1 and D2 receptors. D3, D4, and D5 mRNAs were less robustly expressed by medium spiny neurons, but still represented a significant receptor component. For example, in SP-positive cells, D3 mRNA was found at relatively high levels in a subset of cells (ca. 38%). D4 receptor mRNA was less common (ca. 25% of cells) and present at lower levels. D5 receptor mRNA was rarely seen in SP-containing neurons. In neurons expressing only ENK mRNA, D5 mRNA was seen at relatively high levels in a subset (ca. 20%), whereas D3 and D4 mRNA were present at lower levels in a largely overlapping subset (20–40%). This pattern of mRNA expression suggests that ~70% of all medium spiny neurons colocalize D1- and D2-class receptors with less than half of the colocalization being attributable specifically to D1 and D2 receptors.

When the focus is on the receptors themselves (rather than their mRNA), some evidence indicates only limited colocalization of D1 and D2 receptors in the same striatal neurons. Hersch et al. (1995) reached this conclusion, using selective immunoprobes for these specific receptors (rather than the D3–5 receptors or mRNA). The D1 probe labeled 53% of cells, the D2 probe, 48%. When both probes were used on the same section, the total of labeled cells came to 78%. This is less than the sum of cells labeled by each probe separately, allowing the possibility that ~25% of cells colocalized both receptors. However, possible errors in the proportion of somatic labeling prevented this being made as a strong conclusion. In a parallel electron microscopic study, a stronger conclusion could be reached that there was no colocalization of D1 and D2 receptors in dendritic shafts or spines. Caillé et al. (1996) reported that only ~50% of striatal neurons could be labeled for D1 receptors, and suggested that this proportion corresponded to the neurons of origin of one of the two classes of striatal output neurons.

Other studies of receptors obtain different results. Shetreat et al. (1996) used fluoroprobes based on D1 and D2 ligands in cultures from rat nucleus accumbens.

Fifty two percent of cells were D1-positive of which 14% were positive for D1 *only*; 53% were D2-positive of which 15% were positive for D2 *only*; 38% of cells colocalized both ligands; and 33% had neither. Aizman et al. (2000) found that labeling of both D1- and D2-class receptors with specific antibodies could be seen in virtually all striatal neurons, both in cultured embryonic cells and in slices from adult rats.

In these experiments, the projection target nuclei were not positively identified. Several other papers have examined whether identified striatonigral or striato-EP projections contain D1 receptors, D2 receptors, or both. Robertson et al. (1990) found that, in rats depleted of dopamine using 6-HD, striatal neurons identified by retrograde labeling as projecting to SNR could have their c-fos gene activated by administering the D1 agonist SKF38393. Harrison et al. (1990) and Pollack et al. (1993) found that selective destruction of striatonigral cells by suicide transport leads to loss of D1 but not D2 receptors in the striatum. This conclusion was qualified in a subsequent study by Harrison et al. (1995): Selective destruction of striatonigral neurons after injection of the retrogradely transport toxin volkensin reduced striatal D1 receptor numbers to 15% of normal, while D2 receptor number were reduced to 60%. Since D2 receptors are known to be located on a variety of cellular components in the striatum (including cholinergic interneurons), the proportional loss of D2 receptors on projection neurons was likely to have been greater than this, an inference contradicting the postulate of selective localization of D1 receptors to the direct pathway neurons. In the study of Dubois et al. (1986), a less selective lesion in the striatum in rats led to loss of D1 but not D2 receptors from SNR. Barone et al. (1987) also found that a striatal lesion led to loss of D1 receptors in SNR and EP, but did not study D2 receptors. Black and Crossman (1992) injected toxin in the striatum, which led to loss of D1 receptor binding in the ipsilateral SNR, thought to be due to loss of striatonigral projections. In another lesion study in cats (Beckstead, 1988), there was loss of D1 but not D2 receptors in SNR. In disagreement with the hypothesis of selective localization of the two receptor types in the two pathways, both receptor types were lost in EP. Likewise, Rivera et al. (2003) found that D4 receptors (a subtype of the D2 class of receptors) were located presynaptically in striatal terminals in each of pallidum, EP, and SNR, and showed a dramatic decrease in numbers in each of these nuclei after striatal lesions.

In studies where neurons of the direct pathway were identified by retrograde tracing, the evidence is inconsistent. Ince et al. (1997) reported that, in retrogradely identified striatonigral cells, D1 receptor immunoreactivity could be demonstrated in 96% of neurons, but D2 receptor immunoreactivity in only 1%. Yung et al. (1995) observed that axons passing through the pallidum on the way to the EP and SNR could be immunostained for D1 but not D2 receptors. D1-positive terminals were also found in the latter structures. In contrast, two studies (Ariano et al., 1992; Larson and Ariano, 1994) show a high level of colocalization of D1 and D2 receptors in retrogradely identified striatonigral cells, and a similar result was obtained for striatal cells projecting to GPi in monkeys (Nadjar et al., 2006).

There is less evidence of a direct nature showing that neurons positively identified as the origin of the indirect pathway (projecting from striatum to GPe) contain D2 rather than D1 receptors. Beckstead (1988) found only very low levels of D1 receptors in GPe in cats, although D2 receptors were more abundant, and were reduced in

number by striatal lesions. However, in humans, GPe contains a significant number of D1 receptors, although only about one-third of those in GPi (De Keyser et al., 1988; Richfield et al., 1991). In the pallidum of rats D1 receptors were also plentiful, and could also be reduced in number by striatal lesions (Barone et al., 1987). Yung et al. (1995) found very little D2 labeling of axonal projections in the rat pallidum, which does not fit the idea that D2-positive striatal axons project to and terminate in this structure. Nadjar et al. (2006) found that 87% of striatal neurons projecting to GPe could be colabeled for D2 receptors and almost as many (79%) colabeled for D1 receptors. Harrison et al. (1992) conducted an experiment in which a retrogradely transported immunotoxin was injected into the pallidum in rats. This led to a small (17%) loss of D2 receptors in the striatum and no detectable loss of D1 receptors. In view of the smallness of the effect, it is hard to conclude that D2 receptors are located specifically on indirect pathway class of projection neurons. Gerfen (2006) has produced an illustration based on a genetic engineering method where fluorescent markers label cellular components containing D1 or D2 receptor genes. The former label was prominent in striatum, EP, and SNR of mice, while the latter was prominent in striatum and pallidum. However, unless one knows which cellular elements contain the markers, it is unproven that they correspond respectively to direct and indirect outflow pathways from the striatum. The alternative for pallidal segments and SNR, is that they correspond to cell bodies intrinsic to the respective nuclei, which neurons may bear postsynaptic dopamine receptors. This is possible, since there is direct dopamine innervation of both segments of the pallidum (Lavoie et al., 1989) as well as SNR (involving transmitter release from dendrites of adjacent SNC neurons).

In studies using light microscopy, only somatic location of receptors can be identified, which limits the validity of conclusions. Receptor labeling in cellular processes outside the somata, in sites in the neuropil unidentifiable with light microscopy, such as processes of medium spiny neurons, may apply differentially for different receptor subtypes. If there is such selective location of the two receptor types, binding of a receptor found preferentially outside the cell bodies may be undetectable in light microscopy, because the contrast between cell bodies and neuropil is less sharp. The study of Ryu et al. (1994) is relevant here. Nonspecific cell destruction in the striatum by quinolinic acid led to parallel loss of D1 dopamine in both striatum and SNR (reduced by ~70–80%), but D2 receptor numbers in the striatum remain high (reduced by only ~30%). Since quinolinic acid produces nonspecific cell damage but spares axons, D2 receptors may be located largely in afferent axons in the neuropil rather than in cells.

3.4.4.2 Function Studied by Biochemical Methods

Clearly, the evidence for selective localization of D1 and D2 dopamine receptors, respectively, to neurons of origin of the direct and indirect pathways is not beyond criticism. Nevertheless, following the initial evidence suggesting separation of D1 and D2 receptors, in the cells of origin of these two pathways from the striatum, a line of research has achieved prominence which suggests that the two receptor classes act in different ways in the two types of striatal efferent neurons. Gerfen (1992) reported that dopamine depletion in the striatum results in increased ENK mRNA expression

in striatopallidal neurons and decreased expression of DYN and SP mRNA in striatonigral neurons (see also Young et al., 1986; Gerfen et al., 1990, 1991). Le Moine et al. (1990) also note that ENK-positivity in striatal neurons became more prominent after chronic administration of a D2 blocker. These two effects could be reversed with dopamine agonists, but in a receptor-selective manner: D2 agonists reversed the increase in ENK mRNA expression, while D1 agonist treatment reversed the decrease in expression of mRNA for the other two peptides.

The evidence on the action of dopamine receptor subtypes on peptide gene expression is disputed: Morissette et al. (1999) found that ENK expression was inhibited by D2 receptor stimulation (consistent with Gerfen's results). In contrast to Gerfen's results, ENK expression was also enhanced by D1 receptor stimulation, and expression of tachykinin (a peptide group which included SP) was enhanced by both D1 and D2 stimulation. Murer et al. (2000) reported that in D2 receptor-deficient mice, not only is ENK mRNA increased in the striatum, but also SP mRNA was decreased. Larson and Ariano (1994) comment that in these experiments, "inferring functional receptor levels from mRNA abundance may not be appropriate." Likewise, inferring the actions of dopamine in information processing from effects on peptide expression in cells in histological preparations in experiments involving prior drug treatment for a week or more, or permanent dopamine depletion, is highly problematic.

The view that dopamine acts in opposing ways via D1- and D2-class receptors has also received implicit support from neurochemical evidence that production of cAMP in the striatum is enhanced by agonists at D1 receptors but reduced by agonists at D2 receptors. However, the enzyme that produces cAMP—adenyl cyclase—exists in a variety of forms, which appear to have different relations to dopamine receptors and overall function. Lee et al. (2002) studied genetically engineered mice in which the "AC5" form of this enzyme was missing. In control conditions, production of cAMP by striatal homogenates was only slightly subnormal. Stimulation of cAMP production by D1 agonists was markedly reduced, but by no means eliminated. When a D2 agonist was present as well as the D1 agonist, stimulation of cAMP production was prevented in normal mice, but not in those lacking the AC5 isoform of adenyl cyclase. This suggests that the opposing action of the two receptor types on cAMP production does apply to the cAMP pool to which the AC5 enzyme form contributes. However, in terms of locomotor behavior, the AC5-deficient mice retained full ability to be stimulated by D1 agonists.* These results suggest that the pool of cAMP, which activates behavior, is not the largest pool of this intracellular messenger. The larger pool of cAMP, which the AC5 enzyme can replenish, is apparently not responsible for behavioral activation. In any case, from cytochemical studies (Mons and Cooper, 1994), this isoform of adenyl cyclase appears to be present in the majority of striatal medium spiny neurons. There is thus no support for the view that cAMP in different populations of medium spiny neurons is influenced in opposite directions by D1 versus D2 dopamine receptors.

* D2 antagonists, rather than suppressing locomotor activity, actually enhanced it in the genetically engineered mice, and haloperidol could not produce catalepsy. This is best explained not as a postsynaptic action opposite to that of a D1 antagonist (which suppresses locomotion). Rather, the D2 antagonist acts presynaptically to increase dopamine release, an effect, which is overshadowed by behavioral suppression in wild-type mice.

Other evidence (see, e.g., Trugman and Wooten, 1987), based on assessment of 2-deoxyglucose production in various structures receiving projections from the striatum, has been held to show that D1 and D2 receptors exert different actions on neurons of origin of the direct and indirect pathway. However, this evidence also does not give information closely related to neuronal firing, let alone behavior. Whether it assesses excitatory processes, inhibitory ones or both is unclear, as is the relative role of pre- versus postsynaptic change.

3.4.4.3 Function Studied by Electrophysiological Methods

The hypothesis of opposing actions of D1 and D2 dopamine receptors on the neurons of origin of the two pathways has also claimed support (see, e.g., DeLong, 1990) from evidence reviewed above (Section 3.4.3) showing that rates of neuronal firing in GPi and GPe change in opposite directions in both hypo- and hyperkinetic disorders of the basal ganglia, or that selective lesion or inactivation of these two produces opposite changes in motor output. Thus, the changes in hypokinetic parkinsonian symptoms could be the result of increased firing of the inhibitory striatal neurons projecting to GPe and decreased firing of those projecting to GPi. Those in hyperkinetic syndromes could be due to reduction of firing in striatal afferents to GPe and acceleration of firing in those to GPi. The opposite directions of firing rate changes in the two nuclei (in both clinical conditions) are then supposed to arise because of opposite signs of action of dopamine at the respective D1 and D2 receptors. One recent paper supporting this is that of Querejeta et al. (2001): Inhibition in the rat pallidum resulting from striatal stimulation was reduced by intrapallidal injection of a D2 agonist and increased by that of a D2 antagonist. These results imply that presynaptic dopamine D2 receptors on terminals of striatopallidal axons could suppress release of the inhibitory transmitter. However, it is unclear that dopamine acts in this way on such terminals of the indirect pathway. Moreover, most of the electrophysiological evidence referred to in the above reasoning can be adequately explained in another way: Since GPi receives inhibitory projections from GPe as well as directly from the striatum, the opposite directions of firing rate change can be explained without invoking opposite actions of dopamine at the two receptor subtypes, or opposite directions of firing rate change in neurons of origin of the direct and indirect pathways.

Functional evidence of immediate actions of D1- and D2-selective drugs in single cells clarifies the issue. These actions imply local acute changes, not the result of prolonged changes in whole brain dynamics and behavioral function, as a result of prolonged application of drugs, or dopamine depletion *in vivo*. *First*, there is abundant evidence that dopamine has different actions on striatal neurons according to whether it acts by D1 or D2 receptors (although the effects described differ in detail between studies according to the experimental design used). Thus, several studies (Uchimura et al., 1986; Akaike et al., 1987; Ohno et al., 1987) all report that dopamine produced inhibitory effects via D1 receptor mechanisms and excitatory ones via D2 receptor mechanisms. Pacheco-Cano et al. (1996) reported that dopamine (10–100 μM) bath-applied to slices of rat striatum produces a decrease of firing rate and an increase of membrane resistance with reversal potential of approximately −87 mV. The D1 agonist SKF38393 mimicked both effects, and the current appeared

to be a potassium current. The D2 agonist quinpirole decreased the firing rate but did not change the membrane resistance, suggesting that it acts mainly on suprathreshold ion conductances. Cepeda et al. (1993) found that the D1 agonist SKF38393 potentiated the effect of iontophoretically delivered NMDA on striatal cells, while the D2 agonist quinpirole attenuated the effect. Aizman et al. (2000) found that fenoldopam—a D1 agonist—inhibited the Na^+/K^+ pump, while quinpirole—a D2 agonist—activated sodium channels sensitive to tetrodotoxin (TTX). In such evidence there are inconsistencies in the detail, such as whether D1 receptors exert an excitatory or an inhibitory effect (discussed by Surmeier, 2000). However, there is no disagreement that the two receptor types have different actions.

The *second* crucial point is that all the papers just mentioned show that many (and in some cases, almost all) striatal cells give responses to agents with affinity for both D1- and D2-class receptors and presumably colocalize the two receptors classes. Admittedly, as emphasized by Hernandez-Lopez et al. (2000), D2 agonists had specific effects on ENK-positive cells (suppression of L-type Ca^{2+} currents and reduced excitability and spike activity). These responses were not seen in neurons expressing only SP. However, since this was tested in only three neurons, and since, according to Surmeier (2000), only about 20% of striatal cells express SP, but not ENK, there is not a major discrepancy.

Electrophysiological evidence of this sort gives a more direct indication of the effects of dopamine receptors on neuronal firing than does the expression of genes (as assessed by Gerfen), and does not support the idea of strict separation of dopamine receptor subtypes on classes of cells with different projection targets. Apparently, cells containing both types of peptide respond to D2 receptor stimulation.

3.4.4.4 Function Studied by Behavioral Methods

In behavioral terms, it is well established that drugs acting on D1 and D2 dopamine receptors act in synergy rather than antagonistically (Miller et al., 1990). Agonists at the two receptor types, while having qualitatively different effects, both tend to activate behavior or promote the acquisition of active behavior, while antagonists, again with some qualitative differences, generally both suppress active behavior or its acquisition. If the putative opposed actions of D1/D2 receptors on direct/indirect pathways are reflected in behavior (or motor symptoms), one *might* expect D1 agents to have actions the opposite of D2 agents, but this is not observed. Alternatively, if it is taken that dopaminergic control of the indirect pathway through D2 receptors uses one more inhibitory link than that of the direct pathway through the D1 receptor, the opposed action of the two dopamine receptors in the striatum would mean that the two pathways were effectively synergistic. There would then be no need to distinguish the two pathways as far as behavior was concerned. The complex and specialized connectivity of the pathways from the striatum would then be no more than a morphological curiosity.

It is more plausible to suggest that dopamine, via whatever receptors are available, has similar cellular actions on striatal neurons of both pathways, reflected in opposite directions of behavioral modulation by the two pathways. Therefore, under some circumstances, dopamine agonists might lead to behavioral suppression. In fact, while dopamine agonists are generally activators of behavior, this is not the

whole story. Mixed D1/D2 agonists such as apomorphine activate locomotion and rearing in low doses, but at higher doses lead to immobile postures, upon which are superimposed stereotyped licking, sniffing, and gnawing (Miller et al., 1990). As a function of time, the earliest and latest effects of the drug are increases in locomotion, with a "trough" in between, when there is little locomotion but rather stereotyped behavior. In rats with unilateral dopamine lesions given apomorphil, a similar trough is seen in rotatory behavior, preceded and followed by more vigorous rotation away from the side of the lesion (see Miller and Beninger, 1991). These pieces of evidence might be indications that neurons of origin of the indirect as well as the direct pathways are excited by the drug, the former leading to behavioral suppression and the latter to behavioral activation. The evidence of locomotor suppression at the height of apomorphine's action is not to be explained by a specific action at one or other dopamine receptor, since it is seen best with a mixed agonist.

Even when many technical issues are taken into account, and studies using similar methods are compared, there are genuine contradictions in the evidence considered in Sections 3.4.4.1 to 3.4.4.4. It is possible that these indicate some uncontrolled variable. One such uncontrolled variable is the behavioral history of the animal. A variety of approaches have shown that imposing different behavioral regimes can modify the numbers of striatal dopamine receptors. These regimes include repeated restraint stress (Puglisi-Allegra et al., 1991; Cabib et al., 1998; Giardino et al., 1998), handling (Gariépy et al., 2002), and isolated versus group rearing (Gariépy et al., 1995; Hall et al., 1998). The effects described are complex and inconsistent between studies, depending on strain of rats or mice used, striatal region, and which dopamine receptor is under consideration. Thus, a detailed explanation of these results will not be attempted here. The important point, however, is that these effects are produced by imposed regimes lasting one or more weeks. In the pharmacological experiments of Young et al. (1986), Gerfen et al. (1990), and Le Moine et al. (1990) (cited above), the pharmacological agents (dopamine agonists or antagonists, or dopamine depletion) were in action for a similar length of time and are likely to have had a major effect on behavior. It is possible that the changes in dopamine-receptor-mediated peptide expression are not a direct consequence of effects at the receptor itself but a complex indirect effect produced by lasting changes in behavior.

It is admitted that some of the above evidence shows convincingly the segregation of D1 and D2 receptors to striatal neurons projecting to different targets. However, from Section 3.4.3, activity in neurons of the direct versus indirect pathways, having relations to instrumental behavior of opposite sign, will have opposite correlations with active versus inactive behavior. It is quite plausible that the expression of dopamine receptor subtypes in the two classes of striatal neurons are not permanent features of the neurons but are the by-products of these different correlations. It is, therefore, of interest that in studies using cultured neurons (Shetreat et al., 1996; Aizman et al., 2000), where the correlation with behavior can no longer apply, both receptor subtypes are found in the same cells.

3.4.4.5 Synopsis

In this complex body of evidence, there is no consensus about the degree of dopamine receptor colocalization in striatal neurons of origin of direct and indirect pathways.

There is also no agreement about the oppositional roles of D1 versus D2 dopamine receptors on peptide expression. There is much electrophysiological evidence *against* such oppositional roles in the control of firing of striatal neurons of origin of direct versus indirect pathways and behavioral evidence suggests synergy rather than antagonism between the two receptor subtypes. *Overall the claim that the different effects of D1 and D2 receptors are exerted on different classes of striatal projection cells, and with opposite signs of action, is not supported by the majority of available evidence. If it applies at all, it does not apply to the control of behavior.*

3.4.5 Increase versus Decrease of Firing Rate in Neurons of Origin of the Direct and Indirect Pathways

We return to the main question posed at the start of Section 3.4.3.3: How could firing rate changes in the striatal neurons of origin of the direct and indirect pathways produce the observed changes in firing rate in GPe and GPi in hypo- and hyperkinetic movement disorders?

It is quite plausible to suggest that decreased firing in GPe in human Parkinson's disease, or animal models of it, is due to increased firing of the inhibitory striatal cells projecting to GPe. A number of studies directly investigating firing rates in the striatum support this suggestion by showing that striatal dopamine depletion increases the firing rate of single striatal units. This is seen in anesthetized preparations (Arbuthnott, 1974; Schultz and Ungerstedt, 1978; Orr et al., 1986), paralyzed locally anesthetized preparations (Hull et al., 1974; Alloway and Rebec, 1984), and in free-moving animals (Kish et al., 1999; Chen et al., 2001).* Anesthesia reduces the firing rate, sometimes by as much as an order of magnitude, but the differential between intact and dopamine-depleted animals still applies (Schultz and Ungerstedt, 1978; Kish et al., 1999). Parkinsonian states ("catalepsy") can also be produced acutely by administering neuroleptic drugs. This has been shown to increase firing rates of striatal units in anesthetized (Napier et al., 1985) or paralyzed (Rebec et al., 1980) rats, and a similar effect has been reported when the neuroleptic haloperidol is administered iontophoretically (Hu and Wang, 1986). However, the effect of neuroleptic drugs in relation to catalepsy in free-moving animal on striatal unit firing rates has not been properly studied. Haracz et al. (1993) report on the effects of haloperidol in free-moving rats, which lowered striatal unit firing rate below baseline levels, but this was complicated by the fact that the neuroleptic was given after administration of amphetamine, and did not produce catalepsy.

Corresponding to the increase in firing rate, GABA release in the pallidum of 6-HD-treated rats (Segovia et al., 1986; Bianchi et al., 2003) or in GPe of MPTP-treated monkeys (Robertson et al., 1991) is increased above normal, and, simulating this, injection of a GABA agonist into the pallidum potentiates catalepsy produced by systemic haloperidol (Matsui and Kamioka, 1978). Persisting increases in transmitter release generally cause reductions in the numbers of corresponding receptors,

* It has also been reported that, in such experiments, firing rate of neurons in the striatum contralateral to the lesion is decreased, rather than increased as on the ipsilateral side (Hull et al., 1974; Alloway and Rebec, 1984; Kish et al., 1999; Chen et al., 2001).

and decreases cause proliferation of receptors. These generalizations have permitted further evidence to be obtained compatible with the idea of increased inhibitory activity in GPe in parkinsonian models. Pan et al. (1985) reported that 6-HD lesions of the medial forebrain bundle in rats caused a reduction in binding of the GABA agonist muscimol (assessed by quantitative autoradiography) in the striatum and globus pallidus, and the binding of flunitrazepam—another ligand for receptors by which GABA acts—was likewise decreased in GP. Reduction of flunitrazepam binding in GPe has also been reported in MPTP monkeys (Robertson et al., 1990) and in humans with Parkinson's disease (Griffiths et al., 1990). Taken together, these data suggest strongly that in parkinsonian syndromes, the striatal neurons of origin of the indirect pathway *do* fire persistently at excessive rates.

In contrast, the associated idea—that in parkinsonian akinesia, the immediate cause of the increase in firing in GPi is a reduction in the direct inhibitory input from the striatum—has little support. The firing rate of striatal neurons in intact free-moving animals is already low (Hull et al., 1974; Alloway and Rebec, 1984; Kish et al., 1999; Chen et al., 2001). In assessing the absolute firing rate of the principal cells in the striatum under resting conditions, to avoid selection bias, it is best to select just studies which identify cells by their orthodromic or antidromic responses, or by their response to iontophoretic application of glutamate, rather than by their spontaneous activity. In one study, where units were identified by their responses to electrical stimulation of cortico-striatal input (Schultz and Ungerstedt, 1978), the mean firing rate before dopamine denervation was documented as 0.04 Hz, and in another similar study (Orr et al., 1986) 70–80% of cells had firing rates below 0.1 Hz. In both these studies, the animals were anesthetized with chloral hydrate. In a single study using free-moving rats (Sandstrom and Rebec, 2003), units were identified by their responses to iontophoretic application glutamate. Out of this, 72.7% of units were quite silent and the remaining 27.3% had a mean firing rate of 4.85 $\pm$ 0.85 spikes per second. In another study, in free-moving rats (Ryan et al., 1989), where striatal units were identified by antidromic stimulation from SNR, median firing rates were about 0.3 Hz during locomotion and somewhat less during quiet waking. Only 1 out of 18 antidromically identified unit had firing rates in these circumstances greater than 1 Hz. These are low rates of firing. This makes it unlikely that downstream effects, reflected in behavior, could occur if they were to be lowered further by dopamine depletion. This possibility is not completely ruled out: Behavioral effects such as dystonia and locomotor hyperactivity have been produced by injection of GABA antagonists into caudate or putamen of cats (Yoshida, 1991), implying that there is behaviorally influential tonic activity in the normal striatum. Nevertheless, no direct evidence has ever been produced that dopamine depletion could reduce the firing rate in neurons of origin of the direct pathway.*

If a GABA agonist (muscimol), which should decrease neuronal firing to zero, is microinjected into the striatum, it fails to produce catalepsy in rats

* Yoshida (1991) has claimed that caudate unit firing rates fall significantly after production of parkinsonism with MPTP in monkeys, but the manner of selection of units for recording is not explained, and may be subject to sampling bias.

(Scheel-Krüger, 1983). In contrast, injection of NMDA—an excitatory transmitter agonist—into rostral striatum of rats, led to EMG signs of an akinetic-rigid syndrome (Klockgether and Turski, 1993). Likewise, an NMDA antagonist injected into the striatum reverses catalepsy produced by haloperidol (implying that neural activity generating catalepsy at the injection site is partly dependent on tonic excitatory input there) (Kaur et al., 1997). The region for the injections in these experiments was similar to that where injections of the D2 antagonist haloperidol also produced catalepsy (Ellenbroek et al., 1985). Further evidence that catalepsy is associated with increase (rather than decrease) of impulse activity in relevant striatal projection neurons is provided by an older study (Ossowska et al., 1984), in which catalepsy induced by systemic injection of a neuroleptic could be abolished or strongly attenuated by injection of the GABA antagonist picrotoxin into the pallidum. This implies that the pallidum is subject to vigorous tonic inhibition when the animals are in a cataleptic state. One electrophysiological study (Nisenbaum et al., 1986) has shown that striatal unit firing increased after 6-HD, remained high at 4–6 weeks after the lesion if no recovery of aphagia, adipsia, and akinesia occurred, but fell back to normal if behavioral recovery did occur. At this stage of the experiment, further administration of 6-HD or the dopamine antagonist haloperidol increased firing rate back to the previous high levels, again in correlation with reinstatement of the behavioral deficits. The assessment of unit firing rates in this study was done under chloral anesthesia, but since the differential between intact and dopamine-depleted animals applies in both anesthetized and awake animals, it is likely that the correlation between increased firing rate and akinesia applies even in the awake preparation. In view of such evidence, it is hard to maintain that increased firing rate in GPi in akinetic/rigid parkinsonian syndromes is the result, wholly or partly, of decreased firing in striatal neurons of origin of the direct pathway.

It would be interesting to know if the correlation between increased firing rate and akinesia, seen by Nisenbaum et al. (1986), still applies in free-moving preparations, such as that used by Sandstrom and Rebec (2003). It is also predicted that striatal units should show an increase in firing rate during neuroleptic-induced catalepsy. There have been very few single-unit studies conducted of striatal units in neuroleptic-treated free-moving animals. In one such study, in free-moving rats (Kiyatkin and Rebec, 1999), a D2 antagonist had negligible effect on firing rates of striatal units. Units were a representative sample, because they were identified by their showing a response to iontophoretic glutamate (rather than by their spontaneous activity). However, the dose of drug was insufficient to produce catalepsy. In another study (Frank and Schmidt, 2004), haloperidol was used to bring about catalepsy. There was a nonsignificant increase in firing rate compared to controls, but units were identified by their spontaneous activity, and thus, were unlikely to be a representative sample.

There *is* some indirect evidence compatible with a chronic reduction in the inhibitory tone in GPi or SNR in parkinsonian syndromes, which might be taken as support for the Gerfen/Albin model: Pan et al. (1985) reported an increase in muscimol and flunitrazepam binding in EP and SNR, the two targets of the direct pathway. However, in view of the low rates of striatal neuron firing in normal animals, this evidence is more readily explained as a reduction in inhibitory input

from GPe (as suggested in Section 3.4.3.2), which itself is a consequence of the *increased* firing of striatal cells projecting to GPe. Another recent study (Bianchi et al., 2003) claimed to show decreased firing in direct pathway neurons in low-dopamine states: In rats, GABA release was assessed in SNR, in response to microinjection of excitatory amino acid analogs into the striatum. In intact rats, a large increase in GABA release was seen, while in animals depleted of dopamine after 6-HD injection this increase was abolished. In this study, the striatal injection sites were within 1 mm of the pallidum. Perfusate samples were collected every 20 min, and even with such a low-time resolution, onset of the increased GABA release in the unlesioned animals was sometimes seen not for the first sample, but only for subsequent samples after microinjection of the excitatory amino acid. This slow response suggests that the increased GABA release in SNR depended on spread of the excitatory compound to structures beyond the striatum. In normal rats, spread to the pallidum would lead to increased GABA release in SNR from pallidonigral terminals. After 6-HD, *increased* firing in striatopallidal inhibitory pathways would make pallidonigral cells more difficult to activate in this way, and could explain the loss of increase in GABA release. Thus, due to the location of the injection sites the evidence presented is not a convincing demonstration of lowered firing in direct pathway neurons in the lesioned animals. Further experimental analysis of the relation between site of injection, and intensity and speed of onset of the increased release is necessary to resolve the ambiguity.

The debate reviewed in Section 3.4.4 on whether or not striatal dopamine has opposed actions on neurons of origin of the direct and indirect pathways was inconclusive. In view of this one might propose that, contrary to common belief, dopamine acts in the same way on both pathways, so that, in low-dopamine states, there is an elevation in firing rates in both classes of striatal projection cells. This is parsimonious, and not contradicted by any substantial direct evidence. How might this affect unit firing in GPi/SNR neurons? The interplay of influences in these output nuclei is complex. On the one hand, increased activity in the neurons of origin of the indirect pathway, relayed across two sets of inhibitory synapses, together with increased excitatory input from the subthalamus could be expected to increase firing rate. On the other, increased activity in neurons of origin of the direct pathway, together with increased excitation by the subthalamus in GPe neurons, sending increased inhibition to their targets in GPi, could be expected to combine to lower firing rates in GPi neurons. The balance between these forces is difficult to predict, but the complexity of the interactions might explain the inconsistency in reports on unit firing in GPi in low-dopamine states, as discussed in Section 3.4.3.1. However, a principle, which is *not* in dispute, is that overall motor activity levels are negatively correlated with unit firing rates in GPi/SNR. This leads to an unusual proposal: In low-dopamine states of the striatum, the behavioral manifestation should not be unambiguously a hypokinetic state, but should be a varied and complex mixture of hypo- and hyperkinetic symptoms. The implications of this proposal, for low-dopamine states, as manifest in human diseases, feature prominently in Chapter 8.

4 Theories of Basal Ganglionic Function

4.1 EARLY THEORIES

Over the years there have been many attempts to build a theory of basal ganglionic function. Some of these are rather general theories, not formulated in sufficient detail to identify the possible interactions between excitation and inhibition. An early idea, for instance (Kornhuber, 1971), on the basis of clinical and experimental evidence available at the time, proposed that the basal ganglia were involved in generating slow "ramp" rather than more rapid "ballistic" movements (whose control the author attributed to the cerebellum). Particular points in the argument were, first, that movements of the eyes (as well as of other segments of the body) rely on the cerebellum, but those of the eyes, unlike other parts of the body, are not so strongly dependent on the relevant cortical areas (influenced by the basal ganglia). In addition, slow voluntary ramp movements are possible with limbs and trunk, but not with the eyes (while rapid ballistic movements—"saccades"—are possible with the eyes). The assumptions underlying Kornhuber's suggestion have been superseded: Areas of the cerebral cortex—notably the frontal eye fields—play important roles in eye movements, and also involve the basal ganglia. Eye movements are not limited to saccades but also include smooth pursuit, which has some similarities to ramp movements of the limbs. Kornhuber also suggested that most positive symptoms of basal ganglionic disorder are interpretable as signs of deficiency or release of ramp movements of the limbs and trunk. DeLong (1973) provided supporting evidence for this from the study of the motor correlations of single-unit firing in the putamen. However, it was subsequently found that more of the proximal muscles were active during ramp than ballistic movements, so it was not clear whether DeLong's results reflected ramp movements *per se* or just the use of proximal muscles.

Another early theory, discussed by Mink (1996), was that the basal ganglia were involved in *initiation* of movement. This idea was based on the phenomenology of hypo- and hyperkinetic disorders of the basal ganglia, such as the fact that some patients with Parkinson's disease have difficulty in initiating movement. It was not based on knowledge of the circuitry and sign of action of the connections within the basal ganglia. However, although some Parkinson's disease patients may have difficulty in initiating movement, group average simple reaction times (RTs) are not greatly prolonged, nor are they correlated with degree of overall impairment (Daum and Quinn, 1991). In a proportion of subjects RT is well within the normal range (Evarts et al., 1981). These patients' real deficits are in other aspects of psychomotor function. In normal primates, it is a common finding that most neurons of the basal ganglia start to increase their firing rate *after* the onset of electromyographic (EMG) activity in the muscles involved (Anderson and Horak, 1985; Mitchell et al., 1987).

Another more modern theory, also discussed by Mink (1996), is that the basal ganglia are involved in *sequencing* movements. This idea is based partly on some aspects of the motor deficits of Parkinson's disease. In tasks as diverse as writing and walking, initiation of a complex sequence may be relatively normal, but, as the sequence proceeds, movement gradually diminishes in amplitude, resulting, respectively, in "micrographia" and a "festinating gait." Marsden (1987) added more systematic evidence of the same sort: When a composite movement is required, the second movement is slowed and the interval between the different movement components is prolonged. Patients may have greater difficulty in moving body parts in sequence or simultaneously than would be expected from the sum of the two deficits considered separately (Benecke et al., 1986, 1987). Marsden (1987) suggested that the basal ganglia are required to set up the correct motor programs to execute complex simultaneous and sequential movements: "The basal ganglia, acting on a read-out of existing sensorimotor cortical activity, direct the premotor cortical areas to select the correct parameters of the motor programs required for subsequent motor action." Experimental evidence from single-unit studies in monkeys adds to the case (Alexander, 1987; Brotchie et al., 1991b). Responses of putamen or GP units may

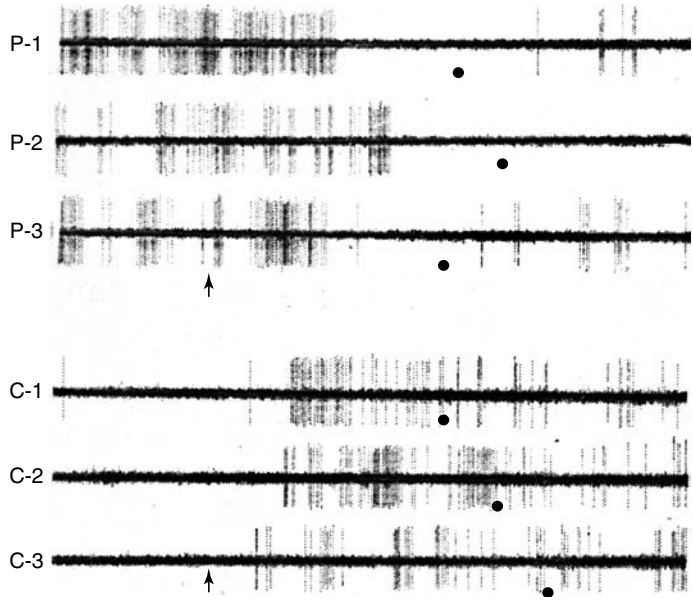

FIGURE 4.1 Neuronal response in advance of a correlated movement response. Delayed response task, with arrow indicating light onset and solid circle indicating response. Each group of three traces represents consecutive trials with intertrial interval of 25–50 s. *Upper three traces.* Pallidal unit (P-1, P-2, and P-3) showing consistent cessation of firing in the middle of the delay period. *Lower three traces.* Caudate unit (C-1, C-2, and C-3) showing consistent increases in unit activity as time from light onset increases, but before the response. (Reprinted from Soltysik, S., *Electroencephalogr. Clin. Neurophysiol.*, 39, 65–78, 1975. Copyright [1975], with permission from the *International Federation of Clinical Neurophysiology.*)

be poorly related to the first component of a composite response, but give better responses in anticipation of the second component, especially if it is predictable. Brotchie et al. (1991b) have suggested that the activity anticipating the second component provides an inhibitory signal to shut off the previous component of a response, while the next is being implemented. However, other papers in fact show that some units in striatum, GPe, and GPi respond well in advance of movement (Soltysik, 1975; Neafsey et al., 1978; Hikosaka and Wurtz, 1983b). An illustration from the paper of Soltysik (1975) is shown below (Figure 4.1). All of these results are in tasks involving responding with a delay or guided by memory of task requirements. Where GP responses lag the EMG responses, the tasks are different, involving an immediate response to a stimulus. In any case, unit responses are not accurately timed-locked to motor response. The best explanation of these data appears to be that units are coding for behavioral strategy rather than specific motor acts including components of motor sequences. If the animal has the chance to prepare a response, units will fire in advance, thus indicating that a behavioral program is activated. If there is no chance to prepare, the overall behavioral strategy may not be engaged until the first automatic motor elements of a response are already being implemented. That this has happened is revealed later by advance firing in relation to subsequent stages of the behavioral strategy.

4.2 SYNOPSIS OF KEY ISSUES

None of these theories attempted to integrate the functional evidence with the emerging evidence on connectivity and sign of actions in the various pathways. More recent theories have, however, been based on the interaction between opposed activation and suppression* influences in the detailed programming of motor coordination and behavioral control. They have therefore tried to present, at least in outline, a neuronal model of the interactions within the basal ganglia. In discussing these theories, two conceptual issues should initially be spelt out.

First, there are a number of possible bases for this opposition of influences. Thus the interaction has been envisaged in terms of (a) the dichotomy between the direct and indirect pathway, the latter having an odd number (three) of sign reversals, the former an even number (two); (b) the supposed differential action of dopamine on the two pathways (the "Gerfen/Albin" hypothesis); and (c) the supposed mutual inhibition between medium spiny neurons in the striatum. The first of these is plausible, in view of the coherent evidence about unit firing in various structures in animal models of hyper- and hypokinetic disorders, a variety of results from experiments involving microinjections of various drugs into component nuclei of the basal ganglia, and evidence from loss of peptides and other markers in Huntington's disease (see Section 3.4.3). The other two proposals are not plausible on the basis of the evidence already considered and for reasons summarized as follows.

The Gerfen/Albin hypothesis is implausible, since, at rest in the free-moving animal, the vast majority of striatal medium spiny neurons have low levels of

* The terms "activation" and "suppression" are used to indicate influences on behavior or motor output. The terms "excitation" and "inhibition" are reserved for synaptic processes.

impulse discharge (see Section 3.4.5). These neurons can thus generate effective signals to downstream target structures mainly by *increase* of discharge rate, not by decrease. Moreover, there is no evidence for decrease in firing rate in syndromes where motor activity levels change. In view of the fact that direct and indirect pathways have opposite net signs of influence on the motor thalamus, there is no need also to invoke opposite signs of action of dopamine on each pathway to produce an interplay between activation and suppression on the CTH network. Thus, not only is the claim of differential effects of dopamine on cells of origin of the direct and indirect pathways empirically unsubstantiated (as discussed above), but it is also theoretically unnecessary.

The view that mutual inhibition between medium spiny neurons could be the basis for competitive interaction between motor/behavioral programs has been advocated in the past by a number of authors, including the present one (Miller and Wickens, 1991; Wickens et al., 1991). When a number of behavioral routines are available, this might be the basis for selection of one program and suppression of the others. Implicit in this idea is that the inhibition from a single medium spiny neuron is distributed to all cells of this class within the reach of its axonal arbor, and, for each such link, the inhibition is so strong that a single neuron can effectively silence all rivals in the neighborhood, and so become the "winner" in a competition between neighbors. Evidence reviewed above (Tunstall et al., 2002; Taverna et al., 2004) shows that inhibition between medium spiny neurons *does* exist, but is weak, and is found in only a fraction of dual impalements of neighboring striatal cells. No reciprocal inhibitory connections were seen in the sample pairs of neurons. Thus, this inhibition probably achieves its normal function not in one-to-one interactions, but as a population effect, where many neurons collaborate in setting the overall inhibitory tone in the striatum (see Section 2.6).

Therefore, in formulating theories of the basal ganglia based on opposition between activation and suppression, we can safely ignore the supposed counterposed actions of dopamine on the two pathways. It is also unlikely that mutual inhibition between neurons in the striatum serves the purpose of program selection, but rather that of "activity control." Overall, it is reasonable to translate the opposition of activation and suppression directly into the interplay between direct and indirect striatal outflow pathways, these having different net signs of action on the CTH network. However, in view of the arguments developed in Section 3.4.1, the "indirect pathway" should be conceived as that from striatum to GPe to GPi. STN appears not to be part of this pathway, but is likely to be a second input nucleus to the basal ganglia from the cortex.

The *second* conceptual issue, which has been hitherto little recognized, is that processes of control envisaged for the basal ganglia are likely to differ greatly if they are aimed at ensuring motor coordination compared with those aimed at selection of behavioral output. *Motor coordination* involves various processes, including segmental spinal or brain stem reflexes with a good deal of use of reciprocal inhibition between agonist and antagonist, the reflexes involved in coordination between limbs (e.g., crossed extensor reflex), and powerful vestibular reflexes to maintain upright posture. Added to this, there are complex cerebellar mechanisms, which, with experience, discover the most efficient way of using muscle activity to control

velocity, and acceleration/deceleration during rapid movements, where inertia and momentum are important considerations (Paulin, 1997). In *behavioral selection*, however, all these are taken for granted as means of implementation of a goal, and the essence of the control involves the relation of the behavioral program to what it achieves for the organism as a whole. A single behavioral program may include a variety of alternative means of implementation, each of which succeeds in achieving the same goal.

It may not be easy to tell which of the two processes—motor control or behavioral selection—is being utilized just from examination of the phenomenology of the emitted motor/behavioral performance. The striatum (as well as other parts of the basal ganglia) has regions easily designated as "motor" (such as the putamen) and other parts designated as "cognitive" (such as the caudate). Moreover there is evidence from primates that the regions of the "motor" thalamus, which receive from the basal ganglia, send their projections not only to prefrontal, premotor, and supplementary motor cortex (Schell and Strick, 1984; Ilinsky et al., 1985), but also in part to the "primary motor" cortex (Nambu et al., 1988, 1991; Inase and Tanji, 1995). However, the consistent use of the term "motor" should not be used to argue against the thesis that the basal ganglia are involved primarily in behavioral and attentional selection, and in favor of their role in motor control in a stricter sense. The term "behavior" can be applied at many levels: Sometimes it involves a single movement at a single joint—even the use of a single muscle. This can be termed "microbehavior." It can also involve more complex behavioral programs (or automatic routines such as those involved in gait) and their selection during preplanning. This is the more familiar use of the term behavior ("macrobehavior"). It merges imperceptibly into attentional selection, as the planning becomes more and more indirectly related to eventual behavioral output. Whatever the level, behavior and its selection is determined by the goal achieved, not by the processes of coordination involved. These comments are especially important in interpreting some of the experimental data on the basal ganglia. The experimental design may have been directed at understanding motor control functions of the basal ganglia, and therefore uses deliberately simplified stereotyped responses. Under these circumstances, only one or a few muscles may be involved. Nevertheless, however simple and stereotyped the responses are, if they have been established by instrumental conditioning procedures, it is likely that they are defined by the goal they serve. They are still under control of the processes of behavioral selection, although they may involve, in parallel, those of motor coordination.

It is arguable that, in normal circumstances, both processes—behavioral selection and motor coordination—are jointly involved in *every* voluntary action, the two occurring in parallel, the former to take decisions about goals, the latter to devise the best manner of implementation of these goals. Nevertheless the two are conceptually quite separate. In many neurological disorders, the normal synergy of the two may be dissociated. For instance, when the means of implementation are disturbed (e.g., by a cerebellar lesion), the relation between a behavioral program and its intended goal may still be preserved, although implemented in an uncoordinated and inefficient fashion. In other neurological disorders (notably, some of those arising in the basal ganglia) motor coordination may be intact, but the relation between behavioral output and goal attainment may be distorted or lost. (This is discussed in Part II of this book.)

Obviously, the role of inhibitory synaptic processes is likely to be quite different for these two stages of the control process. For *motor control* processes there is much use of hard-wired reciprocal inhibition for reflex mechanisms (in functionally antagonist pairs of muscle groups), and inhibitory processes in the cerebellum are also important for determining the exact timing of muscle activations. In these cases, the specific circumstances in which inhibition is employed or removed are not determined by feedback of the overall effect of performance in relation to the goals of the organism as a whole. In *behavioral selection*, however, inhibition is used for selection, rather than in a reciprocal relation matched with (or pitted against) excitation. In other words, the default condition is that no distinct behavioral program (whether active or passive) is emitted (*all* such programs being inhibited), with executive decisions being needed to "unlock" behavioral programs, only one at once, on appropriate occasions. These distinctions become very important in the sections below. They are the sequels to arguments presented in earlier sections, suggesting that the basal ganglia are concerned with selection of behavior according to its significance for the whole animal, rather than with the fine details of input/output programs (such as dealt with by the cortex and brain-stem/cerebellar structures). The theories involving interaction between excitation and inhibition are discussed below. Emphasis will be placed on which of these two types of control are supposed to be mediated by the basal ganglia in each theory.

4.3 THE "SCALING OF MOVEMENT" HYPOTHESIS

One such theory, suggested by DeLong (1990) and discussed both by Mink (1996) and Vitek and Giroux (2000), proposes that convergence of disinhibitory and inhibitory influences (respectively from the direct and indirect pathways) upon the key neurons of the motor thalamus permit "scaling of movement." According to this scheme, the direct and indirect pathways have a "push/pull" relation exerted on the basal ganglionic output nuclei. Increased activity in the direct pathway (or decreased activity in the indirect pathway) causes decreased inhibition from GPi/SNR to be exerted upon the motor thalamus, with release of active movement. Conversely, increased activity in the indirect pathway (or decreased activity in the direct pathways) directed at the same neurons of the output nuclei increases the inhibition from there to the motor thalamus, with the result that active movement is decreased. The details of the balance of these opposing influences on the same neurons determine whether movement is increased (in velocity and amplitude) or decreased.

This hypothesis is consistent with the fact that activity in GPi neurons is usually found to be above normal in an akinetic symptom (MPTP-induced parkinsonism in monkeys) and is below normal in a hyperkinetic disorder (e.g., chorea, dyskinesia, etc.) (Section 3.4.3.1). However, chorea and dyskinesia are not *simply* increases in velocity and amplitude of movement: Voluntary movement may in fact be slowed (Mink, 1996). Moreover it is important to note that the hypothesis of "scaling of movement" refers clearly to an aspect of motor coordination, rather than behavioral selection. Given this, the proposed role of the basal ganglia seems to be redundant, since the cerebellum is concerned with many of the same processes.

The hypothesis also leaves another important question unanswered: The basal ganglia are concerned not only with motor/behavioral output, but also with other processes more in the "cognitive" realm. The cellular structure of the striatum and other parts of the basal ganglia seem to show little difference between regions with motor/behavioral as opposed to cognitive function, and presumably these different regions perform very similar computational operations. The question then is, "what might be the equivalent to 'scaling' of motor processes, as it applies to the cognitive functions of the basal ganglia?"

Finally there is a major difficulty with this hypothesis, in that it requires precise hard-wired convergence upon single neurons in the output nuclei of striatal projections of the direct and indirect pathways. The problem is particularly severe given the relatively restricted distribution of the direct and indirect pathways upon cells in their target nuclei (without the massive divergence typical of the cortex). The riddle of the dynamic operation of the basal ganglia then becomes replaced by another riddle at the level of developmental neurobiology: How could each such precise (nearly "point-to-point") projection of the direct and indirect pathways come to be wired to target exactly the same neurons in the output nuclei?

4.4 THE "FOCUSED SELECTION" HYPOTHESIS

Another hypothesis, discussed by Mink and Thach (1993), and also in the two papers mentioned above (Mink, 1996; Vitek and Giroux, 2000), is identified as "focused selection, and inhibition of competing motor programs." Clearly this hypothesis refers just to the motor domain of the basal ganglia and its corresponding functional circuit. However, even allowing this necessary limitation, the exact terms in which this hypothesis is couched are important and deserve critical scrutiny.

In the scheme of focused selection, according to Vitek and Giroux (2000),

> focusing of motor activity is proposed to occur via activation of the 'direct' pathway, reducing GPi/SNR output, thereby disinhibiting movement-facilitating thalamic neurons ultimately resulting in activation of *prime mover muscles* and execution of the desired movement. At the same time activation of different GPi/SNR neurons by the 'indirect' pathway would increase GPi/SNR output thus increasing inhibition in a population of thalamocortical neurons, which suppress *antagonistic movements* (similar to the mechanism of surround inhibition). (Italicization added by the present author.)

This quotation refers on the one hand to "prime mover muscles" and on the other to "antagonist movements." In other words, it equivocates on one of the key issues mentioned above. One may well ask whether the focused selection theory is a scheme for coordination of muscles which can then be used to implement any of the organism's purposes or intentions, or, alternatively, is a means of selecting that strategy of behavior which explicitly fulfills one of those purposes or intentions, employing a wide variety of alternative schemes of coordination, as is appropriate to the circumstance. Arguments have already been presented in favor of the latter of these two options (including evidence mentioned in Section 2.1 that neurons in the striatum or GPe/GPi rarely represent the activity of muscles, but more commonly represent movements with specific intentions).

The same equivocation can be detected in the account of this hypothesis by Mink and Thach (1993), despite the title of the paper ("Basal ganglia intrinsic circuits and their role in behavior"), as can be discerned in the following quotation:

> In monkeys trained to perform movements by either increasing the activity of a loaded agonist muscle or decreasing the activity of a loaded antagonist muscle, pallidal lesions caused the greater disability [greater slowing of movement] when the loaded antagonist activity had to be decreased. From these studies it appeared that pallidal ablation resulted in a difficulty in inhibiting *unwanted muscle activity* and possibly *unwanted motor programs in general*. (Italicization added by the present author.)

Again, it is of critical importance in theorizing on the functions of the basal ganglia to specify whether pallidal inhibition is envisaged to suppress muscle activity or unwanted motor programs. Even the phrase "motor program" requires further analysis. The question is begged: "What is a 'motor program'?" Is it a scheme of coordination of muscles that can be used to implement any of the organism's purposes or intentions? Or is it a strategy of behavior, which explicitly fulfills one of those purposes or intentions, employing in the process a wide variety of alternative schemes of coordination, as is appropriate to the circumstance?

In a later paper Mink (1996) further develops the idea of focused selection and inhibition of competing motor programs.

> A large number and variety of MPGs [motor pattern generators] must gain access to the motor neuron pools in order to produce posture and movement. Prior to the final common pathway, the various MPGs may act through common descending pathways and interneurons in the brainstem and spinal cord. Activation of these pathways by one MPG may produce an action that is in direct competition with the action of another. Simultaneous activation of competing MPGs would result in ineffective action and cause inappropriate muscular co-contraction and abnormal postures and movements. Consider the example of reaching to pick an apple from a tree. If the output of MPGs involved in maintaining the body upright against gravity cannot be inhibited for the reaching arm, the voluntary movement of that arm will meet resistance from mechanisms that are trying to keep it in place.
>
> In addition to the inhibition of mechanisms that are active prior to the voluntary movement, in many cases it is also necessary to inhibit mechanisms that might be activated by the movement itself. Consider the transcortical stretch reflex which acts to maintain limb position against displacement. If the arm is displaced from a maintained position, the transcortical stretch reflex is activated to resist the perturbation and return the arm to its initial position. ... The transcortical reflex ... must be inhibited ... or it will ... interfere with the ability to make the movement rapidly and efficiently.
>
> As a second example, consider mechanisms that are involved in maintaining the body upright in space. These mechanisms are many, including long-latency stretch reflexes, propriospinal and vestibulospinal mechanisms. If a subject stands on a platform and that platform is suddenly moved backwards, there is a stereotyped sequence of muscle activity in the legs and back that maintains the body upright and prevents the subject from falling. If the subject now sits and makes voluntary movements involving ankle rotation such as depressing the accelerator of a car or the pedal of a sewing machine, activation of upright postural mechanisms by the ankle rotation would interfere with the desired movement and might prevent it from occurring altogether. (Reprinted from Mink, 1996. Copyright [1996], with permission from Elsevier.)

In these passages, the term "motor pattern generator" is somewhat equivocal. Nevertheless, the language used is clearer than in the previous ones, being descriptive more of behavior rather than of motor coordination. It is also very plausible to suggest that, in selection of a specific behavioral program to be performed, not only do competing programs for other behaviors need to be inhibited, but also inhibition of high-level reflexes may be needed. In this context, it is pertinent to point out that some of the inhibitory connections from basal ganglionic output nuclei are directed to brain-stem structures such as the pedunculopontine nucleus (PPN) and the superior colliculus (see Section 8.7.1) rather than the motor thalamus.

Another important mental image in the "focused selection" hypothesis is what is called a "functional center-surround configuration" or (in the words quoted above from Vitek and Giroux, 2000) a relationship "similar to the mechanism of surround inhibition." Mink and Thach (1993) explain this as follows:

> When a voluntary movement is initiated by neocortical (and cerebellar) mechanisms, a corollary discharge is sent from motor areas of the cortex to STN and then to GPi to cause the surrounding majority of pallidal neurons to increase activity to inhibit the targets that would otherwise compete with the selected motor program. Simultaneously, another corollary signal is sent to striatum and then to GPi to inhibit a specific population (center) of pallidal neurons ... Basal ganglia act in parallel to enable selected programs and to inhibit potentially competing programs.

The phrases "center-surround" and "surround inhibition" are borrowed from sensory physiology. However, there is an important difference between "center-excitation/surround-inhibition" relationships seen in many sensory systems and the relationship implicit in focused selection by which the basal ganglia are envisaged to select one among many competing motor/behavioral programs. It is important to be specific about this difference, because it helps in developing the hypothesis of focused selection into a more precise theory.

In the "center-surround" relation, a spatial array of neurons represents a one- or two-dimensional sensory surface. The default condition for functional operation is "no excitation" (no stimulus). When a stimulus does occur it produces excitation involving (in mammalian sensory systems) several closely spaced neurons in the array, also generally excitatory in function. Activation of this group of cells then disperses inhibition to neurons surrounding those initially excited, in principle disynaptically, by way of inhibitory interneurons. As a result, a single neuron in the array will receive excitation from a patch in the center of its receptive field and inhibition from spatially surrounding regions of the sensory surface. The separation of excitatory from inhibitory regions is ensured by two features of the neural networks involved: (a) the matching of neighborhood relations between the sensory surface and the neuronal array, and (b) the fact that the spatial dispersion of excitatory influences (by divergence of the afferent pathway, or local collaterals of the excited neurons) is less than that of the disynaptic inhibitory influences. These two morphological principles make possible a parsimonious account of the connectivity in sensory systems, because, once these principles are built into the neuronal architecture, there is little further need for genetic specification of the detailed targets of each and every neuron.

The phrase "focused selection" seems also to imply real spatial relationships between center and surround. However, if the center–surround relationship is to be used to describe functional connectivity in the basal ganglia, it must be to some degree an analogy or a metaphor, rather than an exact explicit statement, since there is no clear one- or two-dimensional surface to be represented: Even if, for the sake of argument, we are talking about *motor coordination*, and therefore of the layout of the muscular apparatus, there is no clear two-dimensional layout, though there is a much more complex set of spatial relationships between muscle groups in varying degrees of synergy or antagonism with each other. If, more realistically, we are talking of *selection of behavior*, the idea of a spatial layout of neurons whose "neighborhood relations" somehow matches that of the many possible programs for outwardly directed behavior is even harder to envisage, even as a vague metaphor. Without the matching of neighborhood relations between neuronal arrays and what they might represent in the peripheral parts of the body or in the environment (such as occurs in sensory systems), the parsimony of information required to specify connections is lost. The central question about how connectivity is specified is begged, with no obvious answers in sight. It is possible that the model on which "focused selection" is based confuses spatial relations with the more abstract relations of mathematical sets (as captured in "Venn diagrams") regardless of actual spatial relationships.

There are also other questions concerning the specification of connectivity, raised by Mink's (1996) account of the focused selection hypothesis. If focused selection is envisaged to achieve selection of one muscle group for activity, and an antagonist group for suppression of activity, one must ask: How do quasi-point-to-point projections of direct and indirect pathways come to be so arranged that they target neurons controlling specific antagonist pairs? The alternative is that movements and their intentions, rather than muscles are selected. In this context Mink envisages that, in suppressing unwanted movements, two different routes of the indirect pathway are involved, that from striatum to GPe to GPi and that from striatum to GPe to STN to GPi. If the scheme is to work as Mink envisages, signaling via these two routes should always target the self-same neurons in GPi, contributing together to the disinhibition of these neurons in the output nuclei. Connections of both pathways should completely avoid influencing other neurons in GPi, which are subject to inhibition (rather than disinhibition) via the direct pathway. Again there is a requirement for an arrangement of very detailed connectivity (correlated between two pathways and nearly point-to-point) involving several structures of the basal ganglia, which can hardly be described as parsimonious in its requirement for genetic specification.

We are thus led towards the following conclusions: If the basal ganglia are concerned with motor coordination, major questions are begged about how specific connections can be established for all the exact details that need to be coded in connections. Such exact connectivity is unlikely, and is apparently redundant, since it is represented also at brain stem/spinal cord level. In contrast, if the basal ganglia are concerned with behavioral selection, one might think that there is also still a problem about exact connectivity, to ensure that the right striatal output lines target the appropriate thalamic control points.

A hidden assumption of these debates is that there exists precise connectivity between striatal cells (of either the direct or indirect pathway) with exactly the right

neurons in their target nuclei. However it is worth referring to the issue raised by Braitenberg and Schüz (1989), in the context of cortical connectivity. Is that connectivity characterized by "high order or the greatest possible disorder" (in German: "Hohe Ordnung oder grösstmögliches Durcheinander"). The same issue has been mentioned by Szentagothai (1978) and Schüz (1992). The answer of Braitenberg and Schüz favors the second of the two alternatives. This certainly requires less genetic information for specifying connections than hard-wired high point-to-point order. This answer could apply not only to the cortex but also to the basal ganglia. Therefore, let us consider, as a provisional step, that the details of behavioral control are determined not by preordained connectivity, which is targeted in fine-grained detail with such exquisite accuracy that it can deal with every contingency. If we bear this in mind, the alternative may also be suggested that pathways controlling behavioral output are selected from a rich repertoire of connections, even one with much randomness in the detail, by the *effect* of emitted behavior. Already we have strong reason to believe that the basal ganglia are intimately involved in instrumental conditioning. In instrumental conditioning, the effect of behavior and its influence on reinforcement systems selects responses. In neural terms it is also likely to select synapses, neurons, and pathways. With feedback from the effect of behavior, mediated by the dopaminergic (and other) reinforcement systems, just those output pathways are chosen (from a versatile somewhat disorganized all-purpose repertoire of connections), which produce favorable outcomes.

This proposal has the implication that a precise hard-wired somatotopic organization should not be characteristic of the structures of the basal ganglia. In the input nucleus of the basal ganglia—the putamen, "motor" part of the striatum—Alexander and DeLong (1985) have described somatotopic organization of unit responsiveness and microexcitable zones. However, it is a relatively loose form of somatotopy, at the level of whole limbs rather than single joints, without differentiation between distal and proximal limb segments. In the pallidum, Iansek and Porter (1980) reported that cells with similar representation of movement are found in several clusters within the motor region of GP. However, somatotopic layout was not demonstrated, and 29% of cells showed relations to movement on both sides of the body. DeLong et al. (1985) describe a general somatotopy of movement-related discharge in the pallidum, which included some cells located in regions exceptional to the overall trend. They found no evidence for separate representation of different parts within a limb. Overall the evidence for precise somatotopy is slender, and does not contradict the idea that, via the mechanisms of instrumental conditioning, pathways serving motivationally favorable behavior are selected and used wherever they can be found. In their discussion Iansek and Porter (1980) suggest that there is great functional reserve in GP (considered bilaterally). They use this idea to explain previously documented facts, that small GP lesions have little effect on movement, and major impairment is detectable only with large bilateral lesions of GP. Such great functional reserve is exactly what would be expected if the connections through GP constituted a "repertoire" of pathways, to be used in whatever way is possible in the service of instrumental behavior.

This monograph started by defining executive functions. They are concerned not only with selection of behavior (both micro- and macrobehavior), but also with selection of attentional focus, even when there are no immediate behavioral consequences.

Motivational and emotional selection is also brought into the scheme of the basal ganglia, developed by Alexander et al. (1986, 1990). There is much evidence in favor of unifying all these aspects of function, especially in humans, although they use different circuits through the various nuclei of the basal ganglia. In primate species, the striatum is topographically divided into the putamen, which has sensorimotor functions, and the caudate nucleus, connected primarily with the prefrontal cortex, and thought to serve cognitive functions. Despite the fact that there is only a slender gray matter bridge of continuity between these two parts of the striatum, they have almost identical cytology and neurochemistry and presumably accomplish similar computations on whatever signals their afferents deliver. Most of the disorders of the basal ganglia in humans, which are manifested by abnormalities of movement, are frequently accompanied by abnormality in the cognitive domain (see Part II). One of the advantages of the nascent theory of the basal ganglia outlined above is that it easily allows generalization between sensorimotor and cognitive domains. In contrast, if one tries to force the evidence to fit a role of the basal ganglia in motor coordination, it is not at all clear how cognitive processes such as selection of attentional focus can involve computations equivalent to those in the motor domain.

Overall, the problems of pathway selection through the basal ganglia become soluble, at least in principle. Indeed, these problems have already been discussed (Sections 2.3 through 2.5) in so far as they apply to the direct pathways from striatum, which inhibit output nuclei of the basal ganglia. However, it is still needed to explain how these principles apply to the indirect pathways, which disinhibit the neurons of the output nuclei.

4.5 A MORE COMPLETE VERSION OF THE "FOCUSED SELECTION" THEORY, INCLUDING PREDICTIONS

It is necessary to emphasize that both types of medium spiny cell (viz. the cells of origin of both the direct and indirect pathways) *are* spiny neurons, more or less identical in structure. Dendritic spines have been held to be the morphological signature of a class of excitatory synapse, which is capable of plastic change (strengthening or weakening) with such changes being specific to synapses made with a specific spine (Wickens, 1988). This suggests that the excitatory axospinous synapses made on the neurons of origin of both the direct and the indirect pathways are modifiable in similar ways and with similar specificity.

Evidence discussed in Section 2.1 shows that there is a variety of synaptic modification in the striatum, which is dependent on dopamine as a cofactor, specifically involving D1 rather than D2 receptors (Calabresi et al., 2000; Kerr and Wickens, 2001). The controversy over segregation versus colocalization of D1 and D2 receptors was discussed in Section 3.4.4. There is no reason to believe that dopamine-mediated synaptic plasticity in medium spiny neurons applies only to one subset of medium spiny neurons (such as the cells of origin of the direct pathway).

In Section 2.1, the following suggestion was made: "Patterns of activity relayed from the many widely distributed cells in the cortex to the striatum determine that striatal principal cells are brought to the 'up state' in which firing can occur. The cortical cells comprising each pattern will acquire enhanced synaptic effects on striatal

neurons if their behavioral consequences (as a result of their downstream impact on the CTH network) turn out to be motivationally favorable. The most obvious way in which this might happen is if the downstream impact is to release from inhibition a cell assembly governing some strategy of *active* behavior with favorable consequences." In so far as this statement concerns active behavior, it can now be referred specifically to the direct outflow pathways from the striatum. An alternative to this was hinted in Section 2.1, namely that *suppression of activity* in the CTH network could be produced (in assemblies which would otherwise be activated) if this too has motivationally favorable consequences. Thus, among the complex network of direct and indirect pathways from the striatum which, respectively, can inhibit or disinhibit tonic activity in the output nuclei of the basal ganglia, one has a repertoire of connections which in principle could allow any cell assembly mediating active behavior to be either released into activity or to have its activity suppressed. All that is required is that the behavior-mediating cell assembly should have representative neurons in the motor thalamus. Since the patterns of connectivity in both the direct and indirect pathways are of the "multiple alternative point-to-point" variety, both release and suppression of active behavior could be quite specific. Overall, the role of synaptic plasticity of excitatory synapses in the striatum, controlled by activity in the dopamine pathways, which feedback the effect of behavior, is to select polysynaptic pathways through the basal ganglia. These can be of either net sign (i.e., producing either activation or suppression of pieces of behavior) according to the situations in which either of them can deliver motivationally favorable behavioral outcomes.

In many examples of instrumental behavior, both the direct and indirect pathways would be involved *simultaneously* to produce behavior with favorable outcomes, the former generating active components, the latter the concomitant suppression of unwanted behavior. In such cases, it would be difficult to observe experimentally the distinctive role of the indirect pathway. Nevertheless, there are some experimental results in which indications of the competing programs are revealed after lesion or inactivation of GPi. In baboons, Beaubaton et al. (1981; see also Trouche et al., 1984) showed that lesion or inactivation by cooling of GPi significantly reduced RT. Actual movement time was however increased, and responding became less accurate. Selective inactivation of GPi has also been reported to produce dysmetric drifting away from a previously reinforced target position (Hore and Villis, 1980; Mink and Thach, 1991b*; Inase et al., 1996; Kato and Kimura, 1992). Such drifting was shown by Inase et al. (1996) to be due to definite muscle activity (with EMG activity; and tonic activity in pallidal-receiving parts of the thalamus). Thus in the normal state, the intended positional stability seems to be ensured by curtailment of GPi output to the thalamus in a few highly specific connections; and such focused intention is lost when that output as a whole is compromised. In a subsequent study (Wenger et al., 1999), where the task involved reaching for, grasping, and then retrieving a food reward, muscimol injections into GPi led to slowing of the reach component, while the retrieval component was usually accelerated. This was interpreted as reflecting a difficulty in inhibiting the posture-holding mechanisms active before the reach, but which assisted

* This paper also reported that inactivation of GPi produced cocontraction of agonist and antagonist muscles. However, Kato and Kimura (1992) suggest that this was due to spread of drug effects to neighboring GPe.

the retrieval phase. These syndromes may appear to be disorders of motor coordination, but in view of other evidence, discussed above, it is better regarded as a failure of behavioral selectivity, and loss of the specific relation of basal ganglionic output to behavioral purpose. However, one must admit that in such examples of simultaneous activation of one program and suppression of others, it is not clear to the skeptic that one is dealing with behavioral selection rather than motor coordination.

Under what behavioral circumstances *could* one observe the channeling of activity into the striatal neurons of origin of the indirect pathway associated with behavioral suppression? We receive a clue to this from some of the techniques used to produce the various behavioral responses in electrophysiological studies of unit activity in the basal ganglia: The techniques employed are generally various paradigms of instrumental conditioning. This fact is not emphasized, because the conditioning techniques are seen just as a "means to an end," that end being to produce a reproducible, standardized piece of motor/behavioral output. This in turn reflects the fact that investigators have been concerned more with studying neural correlates of coordination in a standardized motor act than with the process of conditioning or the behavioral characteristics of the acts performed. However, instead, if we focus on the prior process of conditioning, it is clear that suppression of behavior is involved in many ways.

The true role of basal ganglionic output might be more clearly observable in instrumental paradigms, where one can separate the times of behavioral activity from those of behavioral suppression. Thus, the special role of the indirect pathway may be seen more clearly when suppression of behavior is the explicitly rewarded response (a "passive" response). Sometimes such response suppression is the "primary" response, while at other times it is but one component in a more complex response pattern, although nevertheless still explicitly trained and rewarded at some stage of the conditioning process. In principle, since the default condition is for the output nuclei of the basal ganglia to inhibit all behavior, the inhibitory effects of neural activity in the direct pathway are superimposed on this to produce active behavior. The action of the indirect pathway to disinhibit (via GPe) becomes an option, only when a habit has been acquired in this way for such active behavior. Therefore, one would expect the role of the indirect pathway to be displayed particularly in suppression of previously acquired active behavior or in "holding-back" performance of a piece of active behavior until a specific imperative signal is given.

Among the behavioral paradigms, which this includes, are the following: (i) passive avoidance conditioning, especially if it involves suppression of a previously acquired active response. For instance, an animal that has been trained to cross from one compartment of a cage to another to obtain food may then be trained to stay in the first compartment by delivering painful shocks if it crosses to the second compartment. (ii) In the "Go-NoGo" paradigm alternative signals are delivered to indicate that reward may be obtained either by making an active response or by suppressing the tendency to such a response. (iii) In the "fixed interval" (FI) schedule of operant responding, the animal is rewarded only for responses occurring more than a given time interval after the last reward. In this paradigm, animals will learn to suppress responding until the end of the latest FI approaches, when responding accelerates ("FI scallop" in a plot of response rate versus time) (see, e.g., Staddon and Innes, 1969). A similar paradigm is the "differential reinforcement of low rates" (DRL).

(iv) In "delayed response" tasks an instructional signal is given indicating the nature of the response to be made, but only after a delay is the "imperative signal" given to actually make that response. During the delay, responding is to be suppressed. (v) "Delayed alternation," for instance, with a choice of pressing two levers, also involves periods of response suppression, ultimately encouraged by reward contingencies. Last, during (vi) extinction or (vii) reversal of a previously acquired active response, response suppression is one of the processes of behavior modification involved during acquisition of the task.

The hypothesis that the pathways for releasing active behavior are different from those that restrain active behavior leads to a prediction for a behavioral experiment. In training an animal to perform a Go-NoGo task, it could be arranged that the initial training in the "Go" component occurs slowly over a number of trials, and likewise that the learning in the "NoGo" phase, to suppress responding, also occurs over a number of trials. With such a basic learning schedule, an animal could be trained over a series of Go-NoGo reversals. If learning to suppress an active behavior involves weakening connections in the same pathways as are strengthened during prior learning of the same active behavior, there should be no progressive improvement across the series of reversals. In contrast, if as hypothesized here, different pathways are used for the active task and for its suppression, the rate of learning of each stage should progressively increase across a series of reversals. This would be shown as a fall, across reversals, in the number of trials to criterion, eventually reaching the point where the reinforcement contingencies in a single trial are sufficient to inform the animal whether the "Go" or the "NoGo" contingency is in operation. This has not been investigated often, but the paper of Sasaki and Gemba (1989) contains behavioral evidence in support of the prediction.

A specific role for GPi in promoting active behavior is suggested by behavioral experiments in rats of Baunez et al. (1995). The task involved lever release within a time limit after appearance of a visual stimulus. Premature responses had to be suppressed, since they would not be rewarded. However, lesions of STN led to an abundance of premature responding. These lesions are known to reduce tonic firing in both GPe (pallidum in rats) and GPi (EP in rats) (Hamada and DeLong, 1992; Nambu et al., 2000). It is likely that the premature responding reflects reduced inhibitory activity in the pathway from GPi to the motor thalamus. The experiment of Baunez et al. (1995) thus provides evidence compatible with a specific role of curtailment of activity in GPi in release of active behavior. However, since STN projects to both GPe and GPi, the result is ambiguous. Selective inactivation of excitatory transmission by local introduction of glutamate antagonists into GPi or GPe would provide a more exacting test: Only inactivation in GPi should release premature responding.

Apart from purely behavioral experiments, some indication that the reasoning developed here is correct comes from older literature about the effect of striatal lesions on paradigms of conditioned behavior. As expected, these lesions prevent performance of recently conditioned active behavior. This includes active behavior in appetitive learning (Thompson and Mettler, 1963; Hansing et al., 1968; Olmstead et al., 1976; Olmstead and Villablanca, 1979), escape learning (Thompson, 1959; Thompson and Mettler, 1963; Kirkby and Kimble, 1968), one- (Kirkby and Kimble, 1968; Neill and Grossman, 1970; Mitcham and Thomas, 1972; Winocur, 1974), and two-way active avoidance learning (Gomez et al., 1958; Green et al., 1967; Mitcham and Thomas,

1972; Kirkby and Polgar, 1974; Neill et al., 1974). There is also evidence that simultaneous or successive discrimination performance is impaired (Battig et al., 1960, 1962; Olmstead et al., 1976; Thompson et al., 1974), although this is more obvious in difficult than easy tasks of this sort. What is more, such lesions prevent performance of many of the varieties of conditioned response suppression (listed above), including passive avoidance (Fox et al., 1964; Kirkby and Kimble, 1968; Winocur and Mills, 1969; Glick and Greenstein, 1973; Winocur, 1974), response suppression early in each stage of FI responding (Hansing et al., 1968), and in differential reinforcement of low rates (Schmalz and Isaacson, 1968; Neill et al., 1974). Of particular interest is the fact that, in extinction or reversal paradigms, animals with striatal lesions perseverate (Divac et al., 1967; Divac, 1971; Schwartzbaum and Donovick, 1968; Butters and Rosvold, 1968; Kirkby, 1969; Olmstead et al., 1976; Sandberg et al., 1979; Dunnett and Iversen, 1981), that is, they continue with the previously trained active response, when the contingencies of reinforcement are expected to favor suppression of this response (and, for reversal paradigms, its substitution by the alternative response). In a similar way, in passive avoidance paradigms, there is impairment in suppressing recently conditioned active responses (in effect another example of perseveration), although suppression of innate responses (i.e., ones requiring no prior training) is not so markedly impaired (Kirkby and Kimble, 1968; Winocur and Mills, 1969). The difficulty in response suppression in striatum-lesioned animals is also seen when locomotor activity is assessed: Lesioned animals (of several species) tend towards hyperactivity, involving quite abnormal locomotor behavior, in which they walk straight ahead regardless of obstacles, rather than avoiding them in a controlled fashion (Mettler and Mettler, 1942; Turner, 1957; Gybels et al., 1967; Gomez et al., 1958). The possibility raised by such older experiments could be made into a clearer test of predictions made here if it were possible selectively to destroy striatal neurons of origin of the direct versus the indirect pathway. One way in which this might be done is to make use of toxins, which are transported in a retrograde direction from a site of injection (e.g., SNR, GPe, or GPi) to their parent cell bodies (i.e., in the striatum), where they destroy those cells (see, e.g., Chessell et al., 1993). Another possibility, already employed in experiments with simpler behavioral requirements (Sano et al., 2003), is to use immunotoxins that selectively destroy neurons of origin of the indirect or direct pathway.

Some other major predictions can be made for modern experiments. They refer to single-unit recording to be conducted within the setting of behavioral experiments in free-moving animals, rather than in the context of analysis of motor control. The predictions are summarized in Figure 4.2. It is predicted that there will be a dissociation between active behavior and suppression of such behavior in the firing changes in neurons of the direct and indirect pathways. In practice, the most feasible experiments are for single-unit studies in the GPe, GPi, and SNR. During performance of active conditioned behavior, the main response of units in the GPi (EP in rats) and SNR should be suppression of neural activity, while that of units in the GPe should be an increase of neural activity. During behavioral suppression in any of the paradigms listed above, neurons in GPi or SNR should either show no change from baseline, or increase their firing rate, while those in GPe should decrease their firing rate.

A number of studies have been conducted on single-unit activity in the two segments of the globus pallidus, in monkeys or cats performing various motor tasks.

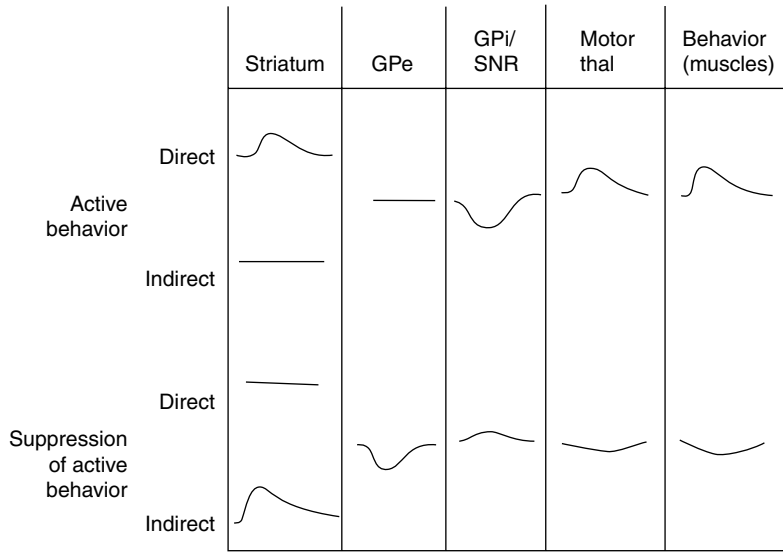

FIGURE 4.2 Predictions for electrophysiological experiments aimed at defining the separate roles of the direct and indirect pathway, respectively, in active behavior and suppression of active behavior. During learned active behavior, it is predicted that unit firing in critical striatal neurons of origin of the direct pathway will rise, that in neurons of GPi/SNR will fall and that in motor thalamus will rise. During suppression of learned active behavior, unit firing in critical neurons of origin of the indirect pathway will rise, that in GPe will fall, and there may be rises in firing rate in GPi/SNR units and falls in motor thalamic units.

The behavioral design of these experiments, and the reporting of firing patterns selectively in GPe and GPi is not adequate to evaluate the above predictions. In general, movement-related neural activity in both segments consists of both increase and decrease of impulse discharge, usually in different neurons, but sometimes mixed. There are a few clues that help in interpreting these data. Neurons showing increases in firing are 2–10 more common than those showing decreases (Lidsky, 1975; Soltysik, 1975; Neafsey et al., 1978; Georgopoulos et al., 1983; Anderson and Horak, 1985; Mitchell et al., 1987; Mink and Thach, 1991a; Cheruel et al., 1994). The predictions for GPe and GPi are mainly about decreases in firing rates related to behavior, as expected, since their controlling inputs from the striatum are inhibitory. It is likely that the increases in firing related to behavior reflect excitation, originating in the cortex, and relayed via STN (see Section 4.7). In a few studies it is revealed that the rarer units, which show decreases in firing associated with movement, have a more exact time relation to movement than the more abundant ones, which show increases in activity (Soltysik, 1975; Anderson and Horak, 1985; Cheruel et al., 1994). In addition, Cheruel et al. (1994) illustrate two units that give a suppression of unit activity time-locked to a reaction time response. When this response was part of a delay paradigm, the inhibition of these pallidal units was also delayed. Pointing in the same direction, a recent study of Sato and Hikosaka (2002) showed that, for neurons in monkey SNR, those which showed response-related decreases in firing had a more specific relation to the direction of the conditioned eye movement than those which

showed an increase in firing. These incidental observations suggest that suppression of neural activity in the pallidal segments may convey more specific information than increases of neural activity. However, experiments conducted to date have not been designed to test the present hypothesis nor the selective role of such coding in each structure in behavioral suppression versus active behavior in GPe versus GPi and SNR. In the proposed experiments discussed above, which explicitly compare active behavior with behavioral suppression, the differing relation to behavior of unit activity in the two structures may be more obvious than in the motor tasks, which have so far been performed. The coding of information in the pallidal segments by inhibitory pauses is discussed further in Section 4.7.

It is also possible to make corresponding predictions for firing changes in striatal cells of origin of projections to GPe versus those to GPi and SNR: The former should show accelerations in firing associated with behavioral suppression, while the latter should show accelerations associated with performance of active behavior (see Figure 4.2). There is in fact one paper, which provides preliminary evidence compatible with these predictions. Schultz and Romo (1992) recorded from striatal cells in monkeys during performance of a pretrained Go-NoGo task. During training, "Go" responses were rewarded, "NoGo" responses were not explicitly rewarded, except that a "rerun" procedure was employed after both erroneous "Go" and "NoGo" trials. Thus the animal needed to refrain from moving in the unrewarded "NoGo" trial before it could perform a rewarded "Go" trial. Of the cells responding transiently to the "Go" or "NoGo" signals, 98/851 (12%) responded to the "Go" signal, 49/851 (6%) to the "NoGo" signal, but only 14/851 (1.7%) to both signals. The occurrence of cells responding during response suppression as well as during active responding suggests that both types of response are orchestrated from the striatum. The relative rarity of single striatal cells responding to *both* signals is consistent with the view that the two phases are orchestrated mainly by activity in two different populations of striatal cells, as envisaged in the preceding paragraphs.*

* In the paper of Schultz and Romo (1992), the proportion of neurons responding to both "Go" and "NoGo" phases of the task was small, but not very different from the product of the proportions responding to each phase alone. Thus, one may argue that there is no evidence from this experiment of strict segregation of cells responding to the two phases, rather than random assignment of behavioral correlations across neurons. This leads us to revisit the question raised in Section 3.2, of whether it is theoretically necessary for neurons of origin of the direct pathway to be strictly segregated from those of the indirect pathway. When this issue was previously raised, much of the empirical evidence suggested strict segregation, but several papers using single axon tracing, and one paper using retrograde tracing in rats left the issue in dispute. Theoretically, however, it may not be critical: Suppose a group of striatal cells are selected by the reinforcement processes because, collectively, and via the direct pathway, they facilitate a particular piece of active behavior. If neurons of origin of direct and indirect pathway are not strictly segregated, these same neurons would also have connections within GPe for the indirect pathway and behavioral suppression. However, it is most unlikely that, collectively, these neurons, selected for the coherence of the active behavior they promote via the direct pathway, would also code for any particular coherent piece of behavioral suppression via their links in the indirect pathway. Furthermore, the potential for confused representation of behavior would be negligible if the number of neurons with ambiguous correlations was small. In the experiments of Schultz and Romo, the neurons involved in either activation or suppression of a particular response were a small minority of all striatal neurons. The proportion of neurons whose behavioral correlation included *both* activation *and* suppression of a specific item of behavior is then so tiny, compared to those specific for one or other phase alone, that they may make little difference in behavioral performance.

The more detailed prediction for the striatum is that these two populations of cells correspond to the cells of origin of the direct and indirect striatal outflow pathways. In practice, experimental test of this is more difficult than the testing of the predictions made about neurons in the pallidal segments or SNR. The reason is that, in the circumstances of a behavioral experiment, there is no easy method of distinguishing striatal cells giving rise to projections to the direct versus the indirect pathway. For instance, identification of cell projections by the antidromic stimulation method is inappropriate in a behaving animal. Labeling of recorded cells for later immunohistochemical analysis of marker peptides would be possible only if the cells had been impaled using glass micropipettes, and this is also not feasible in behaving animals. Nevertheless, other methods may be devised to allow this prediction to be put to experimental test.

There is a less direct form of the prediction for striatal units. The theory developed in this book envisages that the cells of origin of the direct pathway from the striatum increase firing in relation to active acquired behavior, and that cells of origin of the indirect pathway increase firing rate in correlation with *suppression* of acquired active behavior. Cells of both types have been seen in experiments in behaving monkeys performing Go-NoGo tasks (Apicella et al., 1992). Interestingly, those responding during behavioral suppression are rare, unless behavioral suppression in the NoGo phase is explicitly rewarded (compare Schultz and Romo, 1992 with Apicella et al., 1992). Beyond this there are predictions to be made about the effects of dopamine agonists such as amphetamine: Rebec and co-workers (Haracz et al., 1989; Rebec et al., 1991; Wang et al., 1992) have identified striatal units in free-moving rats whose firing rate increases in association with motor activity. Amphetamine enhanced locomotor activity and rearing, and also increased the unit firing rate response correlated with such behavioral activity. One would then predict that firing rate increase in neurons, which is correlated with suppression of activity, would also be enhanced after administration of dopamine agonists. It was mentioned in Section 3.4.4.4 that a mixed dopamine agonist (apomorphine) activates locomotor activity and rearing at the start and end of its time of action, but in between there is a "trough," when locomotor activity is limited and stereotyped behavior occurs. If units could be identified before administration of this agent, which increased firing rates at the time of behavioral quiescence, these same units should exhibit greater increases in quiescence-related firing during the "trough" in locomotor activity while under the influence of apomorphine. Rebec et al. (1997) make observations compatible with this, but falling short of exact confirmation of the prediction. In rats, a group of striatal neurons was identified that increased firing in baseline conditions in relation to head movements, showed no exaggeration of responding in the early phase of amphetamine intoxication dominated by increased locomotion, but did so at a later stage, when head movements from a fixed base were prominent. In this study, correlations between unit firing and behavior were assessed in relation to active behavior, but not in relation to behavioral quiescence. It is, however, possible that this group of neurons increased firing in relation to cessation of locomotion rather than to the active movement of the head. The exact prediction would, however, require quantification of behavioral quiescence or suppression in relation to the actions of amphetamine.

Predictions can also be made for experiments involving microinjection of drugs. Microinjections of GABA antagonists into the rat pallidum (GPe in primates) would be expected to eliminate the influence of increases in firing in the indirect pathway on the pallidum, and so would abolish the signs of behavioral suppression in the conditioning paradigms discussed above. For instance, they should prevent the suppression of responding in the NoGo phase of a Go-NoGo paradigm, leaving the Go responding unchanged. Likewise, response suppression early in each stage in a fixed-interval schedule of reinforcement should be prevented. A similar prediction can also be made with regard to levels of motor activity in rodents treated with apomorphine: The "trough" in activity levels, which intervenes between early and late locomotor stimulation should be abolished by microinjection of a GABA antagonist into the pallidum without abolishing the early and late periods of enhanced locomotion.

Experiments by Amalric et al. (1994) are relevant here. Cats were trained to hold a lever down, and release it in response to an auditory cue. Microinjection of bicuculline into EP prolonged reaction time. Injection of muscimol into the pallidum led to cessation of responding, and that into EP (Amalric et al., 1994) led to an excess of premature responding. Likewise, injection of glutamate antagonists into SNR of rats (Baunez and Amalric, 1996) led to premature responding. Presumably, the inhibitory influence from pallidum to EP or SNR, which is necessary for releasing active behavior, was reduced or abolished by the bicuculline injection in EP, or the injection of muscimol into the pallidum, and was exaggerated by injection of muscimol into EP, or of a glutamate antagonist into SNR. However, the most specific prediction that bicuculline injected into the pallidum should impair suppression of responding (leading to an excess of premature responses) was not confirmed: Such injections had no effect on responding. Since, according to theory, suppression of responding may depend on only a few lines of communication through the pallidum, the injections used may have failed to affect the necessary region of the pallidum. Further experiments of this sort are needed.

4.6 COMPARISON WITH AN EARLIER THEORY OF THE BASAL GANGLIA: SIGNIFICANCE OF CELL ASSEMBLIES

The theories discussed in the above three subsections (viz. the "scaling of movement" theory, the "focused selection" theory, and its suggested amendment) all address the relation between the direct and the indirect pathways through the basal ganglia. Another theory was put forward (Miller and Wickens, 1991), which attempted to address other aspects of basal ganglionic structure and function. This was based on several well-known facts or ideas: (i) that there are recursive loops of connections passing from cortex to striatum, to pallidum, to thalamus, and back to the cortex; (ii) that cortico-striatal synapses are subject to dopamine-mediated synaptic modification; and (iii) that striatal medium spiny neurons give collateral projections by which neighboring cells should be able to inhibit each other. The theory of Miller and Wickens proposed that dopaminergic synaptic modification in the striatum should be able to strengthen synapses, which are critical in allowing specific cortico-basal ganglionic loops to be "closed," thus allowing circulation of activity. Each such specific circuit of connections (including neurons in all components of the basal ganglia as

well as the motor thalamus and cortex) was referred to as a "cortico-striatal cell assembly." It was assumed that this configuration controlled behavioral and motor output. Because the "closure" of each loop was mediated by the dopaminergic reward process, it was implicit that the behavioral outputs each loop controlled had motivationally favorable outcomes. Within the striatum, neighboring neurons, if active, were envisaged to engage in a fierce competitive process: The neuron which was most strongly activated from the cortex would inhibit its neighbors more strongly than they could inhibit it. The net result was a "winner-takes-all" dynamic in the striatum, such that in any one striatal domain only a single medium spiny neuron could be active at any one time. The fierce competition within the striatum necessarily led to competition between different cortico-striatal cell assemblies. This was thought to ensure that only a single behavioral program could be active at one time. Moreover, the scheme generalized from motor/behavioral functions to cognitive functions. With regard to the latter, the competition between cortico-striatal cell assemblies accounted for the possibility of selectivity of attention on one field of information excluding all others.

The present reformulation of the theory of basal ganglionic function, while assimilating the evidence about the direct versus the indirect pathways, has several elements in common with the older theory of Miller and Wickens. However it has some important differences. One of the new facts leading to the reformulation has already been mentioned, that mutual inhibitory connections between neighboring spiny neurons are weak, such that silencing of a neighboring neuron requires converging activity from a number of inhibitory inputs, not just a single one. Moreover, a single medium spiny neuron gives inhibitory collaterals to only a proportion of neighboring cells of this class, rather than all of them, as had to be envisaged in the "winner-takes-all" scenario. An alternative, more plausible role for these inhibitory collaterals has already been mentioned, that is, to limit the total number of neurons in a domain which can be active at once, the resulting number being more than just one, but not a large population. The mechanism suggested is that, if too many medium spiny neurons in a locality become active together, the inhibitory tone carried collectively by all the collaterals will be high, and will act to reduce the number of active neurons back to a level where the striatal output can perform its role without the specificity of its signaling to other components of the basal ganglia being compromised.

Another new perspective offered by the present formulation is that the neuronal interplay envisaged to take place in the basal ganglia is radically different from that thought to occur in the cortex. Thus the term "cell assembly" should not be used to describe the cybernetic operations performed by the striatum or other parts of the basal ganglia. This point can be reached from consideration of several types of information, including morphological, electrophysiological, and functional evidence. One of the morphological points is that the basal ganglia do not constitute a network where complex subnetworks of reciprocally connected neurons can exist. Instead the pathways through the basal ganglia constitute a sequence of stages where communication is mainly unidirectional. Whereas the cortex has a very large potential for convergence and divergence, the pathways through the basal ganglia come closer to the model of a set of alternative labeled lines, allowing point-to-point control along

the sequence of stages. Many lines from the striatum may be afferent to each neuron in GPe or GPi, but it is not necessary for several to cooperate to have a transmittable postsynaptic influence. On these points, the basal ganglia have a style of connectivity completely different from that in the cortex, which allows cell assemblies to form.

Functionally, the evidence from CCHs (Jaeger et al., 1995; see Section 2.4) shows that neighboring striatal medium spiny cells are more independent of each other than are neighboring cortical neurons. This conclusion is supported by quantitative studies of synaptology, which show that the cortico-striatal afferent fibers are distributed so widely and sparsely that neighboring recipient neurons share very few synaptic inputs. The fact that the medium spiny neurons do not communicate by excitatory synapses is another contributory mechanism ensuring the functional independence of neighboring neurons. Such independence is totally different from the relations commonly found in the cortex, which is an essential aspect of the theory of cell assemblies.

It is also clear that (apart from cortical afferents to the striatum and subthalamus, and subthalamic outputs) all major connections of the basal ganglia utilize inhibitory, not excitatory synaptic mechanisms. The modern view of cortical cell assemblies incorporates the evidence that there can be exact temporal structure in impulse trains, including exact temporal correlations between impulse discharges in different impulse trains. Such exact temporal structure implies excitatory transmission to recipient neurons whose integration time is quite short (only a few milliseconds). The inhibitory transmission, which predominates in the basal ganglia, is ill suited to generate trains of exactly timed impulses. This point is reinforced by details of the biophysics of medium spiny neurons. Nisenbaum et al. (1994) showed that depolarizing current pulses evoked a slowly developing ramp depolarization that could rise over several seconds before spikes were generated. This was taken to be due to a potassium current switched on by depolarization and inactivating quite slowly to allow, subsequently, further gradual depolarization. Clearly the time when membrane potential crosses firing threshold is not exactly related to the time of incident EPSPs. Recovery of the potassium current from inactivation, during prolonged hyperpolarization was also shown to be very slow (with average time constant of ~2 s). Thus, in the shift from the "down-state" to the "up-state" the duration of the previous "down-state" should be important in determining the rate of a subsequent rise to the "up-state." Consequently, responsiveness of a medium spiny neuron to excitatory synaptic inputs will be greater if the previous "down-state" has been only brief. Again one must conclude that the timing of excitatory input cannot specify the exact timing of impulse firing in medium spiny neurons. Stern et al. (1997) have shown that, while the timing of down- to up-state transitions is broadly synchronized between neighboring neurons, there is not exact temporal correlation between the individual impulses in neighboring neurons.

The earlier theory (Miller and Wickens, 1991) postulated that the basal ganglia had a role in cognitive functions—that is, control of the focus of selective attention—as well as in motor/behavioral functions. The present theory also generalizes between behavioral selection and the processes of attentional selection. However, in one important respect the earlier theory attributed functions to the basal ganglia

which generalized more widely than the present theory: In the earlier theory mutual inhibition in the striatum was supposed to generate the selection of one out of a number of possible focal points for attention, and of strategies of behavior; but the mutual inhibition was also envisaged to play a part in motor control. Under normal circumstances this was supposed to ensure reciprocal inhibition. In Parkinson's disease, when the mutual inhibition in the striatum was supposed to fail, the result was cocontraction of agonist and antagonist manifested as rigidity. It was also implicit that under certain circumstances, cocontraction of agonist and antagonist might be part of the repertoire of normal motor control again under control of the striatum. In the present theory the latter aspects of the earlier theory are no longer advocated. Behavioral and attentional selections *are* emphasized, while motor control is not seen as one of the functions of the basal ganglia. With this shift of emphasis, the fact that disorders of the basal ganglia often lead to symptoms loosely described as abnormalities of motor control, including rigidity, is an obviously difficult point for the new theory. It is discussed in detail in Part II.

Overall, the functions of attentional and behavioral selection attributed to the basal ganglia fit the concept discussed in Chapter 1—that is "executive control." It is not surprising that the structures providing this control do not use the cell assembly configurations thought to underlie cortical function. Executive decisions imposed on cell assemblies of the CTH network require a style of neural organization quite different from the cell assemblies they control. One can sum up the operations of the basal ganglia as follows: The striatum abstracts a wide variety of patterns from the cortical output, and uses them either to release or to suppress specific pieces of behavior. Each combination of striatal input and behavioral output has, in the past, been evaluated according to whether or not the behavioral activity or suppression has motivationally favorable consequences. It can do the same with regard to either the enhancement or suppression of particular focal points for attention. Having made its evaluation, it uses the result to bias the patterns of activity in the cortex, thus differentiating cell assemblies, which might otherwise coalesce. In psychological terms, a basis is provided for discrimination between two stimuli, which are partly similar and partly different (provided the differences predict motivationally different outcomes of behavior). Without the intervention of the basal ganglia, generalization, rather than discrimination, would always be favored.

4.7 DYNAMICS OF NEURAL ACTIVITY IN STRUCTURES OF THE BASAL GANGLIA AND THE NATURE OF THE NEURAL CODE IN THESE STRUCTURES

Three core structures of the basal ganglia—GPe, GPi, and SNR—are under the control of two input pathways from the cortex, one via the striatum and the other via the subthalamus. As already discussed, the actions of these two input nuclei on the core structures are of opposite sign, the former inhibitory and the latter excitatory. Apart from this important fact there are several other points distinguishing these two input pathways. In general, these differences suggest that the cortico-striatal pathway to the core nuclei conveys a great deal of detailed information, while the

cortico-subthalamic pathway exerts its influence in terms of overall levels of the behavior-related activity it conveys, rather than via detailed patterns encoded within its population of connections. The differences are listed below, with some comments explaining each of them in relation to this functional distinction.

1. The cortico-striatal pathway arises from all regions of the cortex (Parent and Hazrati, 1995b), whereas the cortico-subthalamic pathway arises from restricted anterior cortical regions, such as the primary motor cortex (and other regions involved in planning of immediate motor/behavioral output) (see Section 3.1). Likewise, the striatum is a large structure, suggesting that it can deal with a large flow of information. STN is relatively small.
2. The cortico-striatal connections arise in both lamina V and supragranular laminae of the cortex (McGeorge and Faull, 1989; Gerfen, 1989; Berendse et al., 1992; Cowan and Wilson, 1994), while cortico-subthalamic connections arise only in lamina V (Section 3.1). The supragranular layers are probably involved in the detailed information of cell assembly configurations, while lamina V, in so far as it contributes to cell assemblies, is involved in less specific priming functions (Miller, 1996, 2002). In addition, neurons of laminae V provide output to thalamus, brain stem, cerebellum, and spinal cord (including motoneurons, which form the "final common pathway" for motor/behavioral output).
3. The principal neurons of the striatum are rich with dendritic spines, upon which cortico-striatal connections terminate. Such neurons are not typical of STN (Robak et al., 2000). Dendritic spines are generally considered to be indicative of synapses which can be modified with high selectivity (see, e.g., Wickens, 1988).
4. The pathways from the striatum to GPe, GPi, and SNR have morphological features of very exact connectivity, in which "cross-talk" between alternative "labeled lines" is minimized. Connections from STN to GPe, GPi, and SNR appear to be more diffuse, so that discrete lines of information transmission cannot be defined (Hazrati and Parent, 1992a,c).
5. An electrophysiological study by kolomiets et al. (2001) reported that single cells in the striatum never gave responses on stimulation of two different cortical sites. In contrast, for neurons in STN, convergent activation from different cortical sites was not uncommon.
6. In cross-correlation studies, neighboring striatal neurons show no peaks indicative of a common input (Jaeger et al., 1995), except those determined by the correlated overall shift between up-state and down-state (which are coherent over large blocks of striatal tissue) (Stern et al., 1998). In STN, broad CCH peaks (width 200–400 ms) can be seen, indicative of common input from many cortical neurons, which share broadly similar changes in firing frequency. Poststimulus time histograms in different neurons show more similarity than expected by chance (Ryan et al., 1992). These results suggest that, in the relay from cortex to striatum there is little redundancy of information, while in that from cortex to STN different neurons receive impulse trains with very similar temporal patterns.

These indications of different roles for the striatal and STN inputs to the basal ganglia raise important questions about how the two inputs interact, especially in GPe, GPi, and SNR. An important background fact for this question is that neurons in all three structures have a marked tendency to maintain steady levels of tonic impulse discharge. This can be seen *in vivo*, but the inherent nature of the tonic discharge is seen more explicitly in slice preparations. In these circumstances, when there is no tonic excitatory drive from other structures such as STN, principal neurons in all these three structures show rather regular tonic activity at frequencies of 2–40 spikes/s (see Figure 4.3 and Section 8.6). Depolarizing pulses increase the discharge frequency, but, significantly, after a depolarizing shift, there is little spike frequency accommodation. A given level of depolarization appears to specify a given frequency of firing, regardless of the time elapsed since the depolarizing shift.

In STN, in contrast to the striatum, but like GPe, GPi, and SNR, most neurons are tonically active, a characteristic property also seen in *in vitro* slice preparations. Such tonic activity is itself subject to both excitatory modulation from the cortex and inhibitory modulation from GPe. It is likely that most cells in GPe, GPi, and SNR, most of the time, are subject to a steady, though fluctuating tonic excitatory drive from STN. Given that STN activity is likely to be enhanced during behavioral activity (Wichmann et al., 1994a) one can explain the fact that the majority (60–90%) of neurons in GPe and GPi (see Section 4.3) show enhancement of neural activity related to movement. Presumably those in GPi are the ones which ensure that competing behaviors are suppressed.

In intact animals modulations from the two inputs to the basal ganglia are imposed upon the tonic firing of neurons in GPe, GPi, and SNR. There is an inhibitory input from the striatum (weak in any one input synapse, due to the predominantly low-firing frequency in striatal neurons, but multiplied many times because of multiterminal innervation by each striatal axon). An excitatory input comes from the STN. Consideration of the firing patterns in these two input structures is necessary to define their respective impact on GPe, GPi, and SNR, and the way the two inputs might interact there. Clearly there is a dynamic competition in GPe, GPi, and SNR between the information-rich inhibitory influences from the striatum and the tonic nonspecific excitatory drive from the STN. In principle, this can certainly achieve the quasi-spatial "focusing," which is supposed to release wanted active behavior and suppress unwanted competing behavior. However, the competition may have other equally important roles in the temporal dimension. Nambu et al. (2000) investigated the effect of inactivating STN with muscimol injections. In GPe, before the injection, there was typically rapid irregular firing, with occasional pauses lasting no more than 1 s. After the injection, pauses could last 5 s or more. In GPi before the injection there was typically high-frequency discharge with little pause, but this came to have pauses of 0.5 s or more after the injection (see Figure 4.3). These effects on firing pattern could be taken to imply that, normally, excitation of GPe, GPi, or SNR from STN increases activity so that inhibitory periods controlled from the striatum are kept short. After inactivating the excitatory drive from STN, the inhibitory periods become longer. In other words, by arranging, in the normal case, that the episodes of inhibition driven from the striatum have to compete with tonic excitation from STN, the temporal resolution of the control from striatum is sharpened. The same process

was also shown by Ryan and Clark (1991) in the context of single-unit responses in GPe and GPi to cortical stimulation. Kainate lesions of STN not only prevented the excitatory phases of the response (presumably driven from STN), but also greatly prolonged the inhibitory phase (presumably driven from the striatum). Inherent in these arguments is the idea that GPe, GPi, and SNR code behaviorally significant information not by impulse discharge (whether as an impulse or as a rate code), *but by a succession of accurately timed pauses in otherwise unbroken trains of*

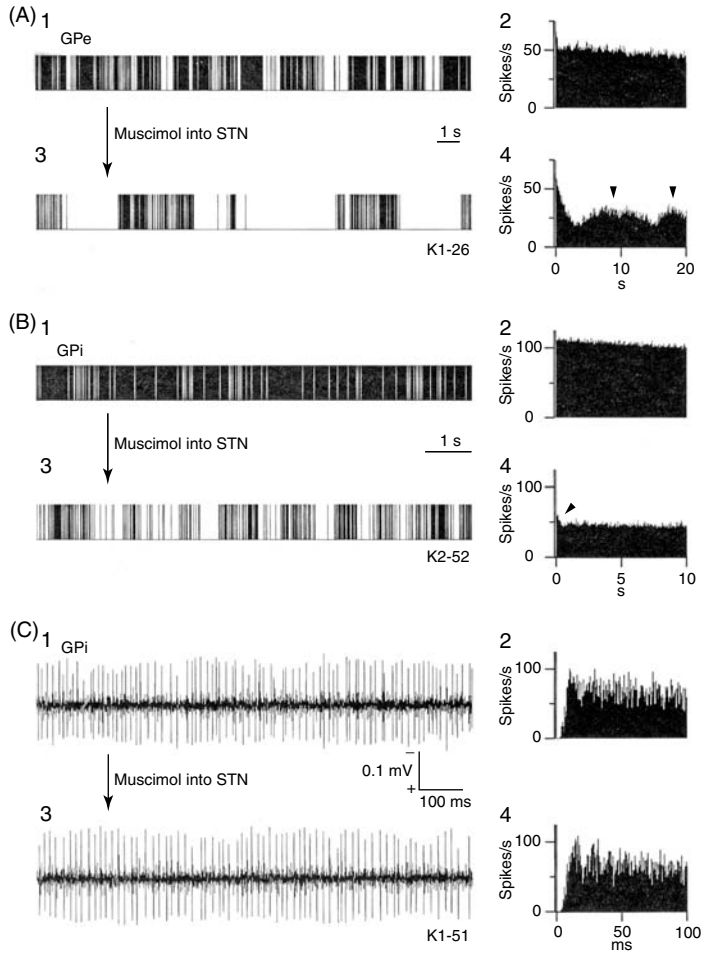

FIGURE 4.3 Experimental results illustrating the coding of information by timing of pauses in firing, rather than by timing of impulses. Units recorded in waking monkey. *Right-hand traces*: Unit firing. *Left-hand graphs*: Autocorrelation histograms. *Upper two traces*(A): Unit in GPe showing tonic firing broken by short pauses of <1 s. After muscimol injections into STN, the pauses lengthened to many seconds. *Middle two traces*(B): Unit in GPi showing unbroken tonic firing. After muscimol injection into STN, pauses of up to 500 ms appear in the trace. *Lower two traces*(C): Same as middle two with faster time base. (From Nambu, A. et al., *J. Neurophysiol.*, 84, 289–300, 2000. With permission from *Journal of Neurophysiology*.)

impulses. The significance of STN is then to provide tonic activation, which ensures that, in the absence of striatal inhibition, there is continuing activity in neurons of GPe, GPi, or SNR. Without this excitatory input, it might not be possible for a clear contrast to be produced in the impulse trains in these structures, between tonic activity and the information-rich pauses in discharge.

There is a corollary to this. Neurons in STN, like those in GPe, GPi, and SNR are inherently active with no spike frequency accommodation after depolarizing current shifts. Like neurons in GPe, GPi, and SNR, those in STN are subject to competing modulatory influences, an excitatory one from the cortex and an inhibitory one from GPe itself. During active behavior, impulse activity in STN neurons is driven to higher rates by the cortical input (Wichmann et al., 1994a). This means that, during active behavior, the inhibitory influences from the striatum exerted upon neurons in GPe, GPi, and SNR have to compete more fiercely with the excitation from STN. This leads to the temporal code of inhibitory pauses coming to have increasingly sharp temporal resolution, as the vigor of movement and consequent STN activity increases (see Figure 4.3). The temporal precision of this code can never be as precise as the impulse code mediated by excitatory transmission in the cortex. However, tonic firing rates *in vivo* in GPe and GPi can range between 20 and 120 Hz. The corresponding temporal resolution of the code of inhibitory pauses might then scale with the reciprocal of these values, namely from 50 ms down to an optimum of ~8 ms.

5 Synopsis of Part I and Predictions Derived from It

A theory of the basal ganglia is developed in Part I. A central feature of this theory is the definition of executive functions (involving decision-making about behavior, attentional focus, and underlying motivational target), and the separation of these functions from both the associative functions of the cerebral cortex and the mechanisms of brain stem, cerebellum, and spinal cord involved in motor coordination. An essential aspect of the theory is thus that the basal ganglia are concerned not with motor control or coordination (as has often been implied in the past), but with these executive functions such as selection of behavioral strategies, foci for attention, and long-term goals. These two functional processes—behavioral selection and motor coordination—generally function together in producing motor/behavioral output, yet, for theoretical reasons, it is suggested that they involve quite separate styles of information processing and neural machinery.

Several facts about the basal ganglia support the proposal that they are involved in executive functions: The fact that the output from the basal ganglia to the motor thalamus is inhibitory fits this role. The role of striatal dopamine as the reinforcement signal in instrumental conditioning is also consistent with this proposal, since instrumental conditioning in the present is closely linked to executive decisions taken subsequently. Also consistent with the proposal is the fact that firing of neurons of the basal ganglia are not closely linked to actual motor acts, but are more closely linked to the intention of those acts. The distinctive manner of connectivity in the various links between striatum and motor thalamus, characterized by "alternative labeled lines," rather than diffuse convergence and divergence, is also necessary for instrumental behavior, since it is necessary for active neurons in the striatum to address specific neurons in the motor thalamus, disinhibition of which releases specific behavior. An associated requirement for this scheme of behavioral selection and instrumental conditioning is that there must be strict limits on the number of striatal neurons activated in each environmental situation, otherwise, release of behavior or attentional focus will not be sufficiently specific for instrumental conditioning to occur. It is proposed that the collateral inhibition between neighboring striatal cells provides an overall inhibitory tone in this structure, resulting in negative feedback control to limit the number of coactive striatal neurons.

Major significance is given to the distinction between the "direct" pathways from striatum to motor thalamus (with two inhibitory links in sequences) and the so-called "indirect" pathways (with three such links in sequence). The conclusion is reached that the version of the indirect pathway, which is actually used for signal transmission, is that from striatum to GPe, to GPi and SNR, and thence to the motor

thalamus. The alternative conceptualization of the indirect pathway, with relays from GPe through STN to GPi and SNR and to the motor thalamus, does not survive close scrutiny. The idea that dopamine acts with opposite signs on the striatal neurons of origin of the direct and indirect pathways is not supported by the majority of available empirical evidence, and is also theoretically unnecessary.

Given this overall scenario, any pattern of information relayed to the striatum from the cortex has the potential to influence the neurons in the motor thalamus (critical for release of specific behaviors, foci of attention, or motivational targets) via either of the two functionally opposite pathways: With two reversals of sign in the "direct" pathway and with three in the "indirect" pathway. Activity channeled in the former and latter pathways releases and suppresses active behavior respectively. Either alternative possibility is selected by the consequences of emitted behavior according to whether release or suppression of a specific piece of behavior turns out to be motivationally favorable. The available electrophysiological evidence in behaving animals does not provide a critical test of these postulates, partly because these experiments have been designed to investigate motor coordination or control by the basal ganglia, rather than behavioral selection. New predictions that would provide critical tests of the present theory are discussed.

The neural code used in the segments of the pallidum, SNR, and the motor thalamus does not give any significance to the precise timing of individual impulses. Instead, information is coded by the timing of inhibitory pauses in the neurons of these structures, a method of coding which, intrinsically, has less temporal precisions than the impulse code thought to occur in the cortico-thalamic networks. For such a code to operate correctly, it is necessary for neurons in GPe, GPi, and SNR to generate tonic trains of fairly regular impulse activity against which the phasic inhibition derived from signals relayed from upstream structures can be contrasted. In part, this tonic activity is intrinsic to neurons of these three structures. However, it is enhanced by tonic excitatory drive from the subthalamus. Because of the input from motor cortical regions to the subthalamus, this excitatory drive can be increased at times of vigorous motor activity. As a result, the contrast between inhibition from striatum and excitation from the subthalamus becomes sharper, and the temporal resolution of the code of inhibitory pauses becomes more precise at times of behavioral performance.

In many respects, the basal ganglia have functional and structural organization quite different from the cerebral cortex. This is evident in the fact that the connections of the basal ganglia are mainly inhibitory rather than excitatory with the result that impulse trains code information in a quite different manner from those in the cortex. The characteristic connectivity of the basal ganglia ("alternative labeled lines") is also quite different from that of the cortex, where the possibility for widespread divergence is maximized. Finally, the dopaminergic input to the striatum appears to be a diffuse signal, which plays a critical role in the cybernetics of that structure, whereas the essence of information processing in the cortex depends on associative algorithms that are local to each pyramidal cell.

There are a few predictions arising in the foregoing chapters. To test these predictions requires difficult experiments, which in some cases are beyond presently available techniques. However, they are rather precise tests of the theory. In Section 2.4,

it was predicted that each neuron in the motor thalamus receiving inhibitory inputs from the output nuclei of the basal ganglia should receive these inputs from just a single cell in the output nuclei with no anatomical convergence. The same prediction can be made for the inhibitory connections from GPe to GPi or SNR. In the same section, it was predicted that impulse activity in single neurons in the parts of the motor thalamus receiving from the basal ganglia should represent goals not movements. In Section 3.4.5, one prediction was made on a question unanswered by presently available evidence: In free-moving rats made cataleptic by administration of neuroleptics, there should be a general increase in firing rates of striatal neurons including neurons of origin of the direct pathway. In Section 4.4 (see Figure 4.2), a number of predictions were made for electrophysiological experiments in behaving animals, about different patterns of change of unit firing in GPe, GPi, and in SNR, in relation to behavioral tasks involving active instrumental behavior and suppression of such behavior. Other predictions were made, beyond the technical limits of current experiments, about changes in unit firing in the striatal neurons of origin of the direct and indirect pathways, again in relation to behavior involving active responses versus suppression of active responses. Further, predictions were made that behavioral suppression, acquired as components of a variety of instrumental paradigms, should be eliminated by blockade of inhibitory transmission in GPe by microinjection of GABA antagonists.

The author is also aware of a number of features of the basal ganglia, not addressed in this theory. These include the significance of the cytological and neurochemical subdivision of the striatum into striosomes ("patches") and matrix. Striatal projection neurons also receive an input from nonprimary thalamic nuclei, which has been reported to target neurons of origin of the direct rather than the indirect pathway (Sidibé and Smith, 1996). The significance of these connections is not clear. In addition, the striatum as well as GPe, GPi, and SNR contain small numbers of interneurons, whose function is not dealt with here. One class of interneurons—the cholinergic cells of the striatum—is obviously very important and becomes a focal point in understanding some of the disorders of the basal ganglia in Part II. These interneurons have distinctive inputs, notably from certain nonprimary nuclei of the thalamus, whose role is also not clear.

Part II

Interpretation of Symptoms of Diseases of the Basal Ganglia

6 Introduction

6.1 GENERAL COMMENTS

Superficially at least, most symptoms of disorders of the basal ganglia appear to be disorders of motor coordination rather than of behavioral selection. As noted above, this fact poses a major problem if, as explained here, it is proposed that the basal ganglia are concerned with behavioral, attentional, and motivational selection, rather than with motor coordination. To resolve this serious difficulty some general comments need to be made before embarking on a more detailed discussion.

It was pointed out in Section 4.1 that the executive decisions included in the term "behavioral selection" can refer to anything from decisions about simple motor acts at a single joint ("microbehavior"), through more complex behavioral sequences ("macrobehavior"), right up to long-term planning and selective attention related only remotely to eventual outward behavior. The different levels of this hierarchy are likely to be represented in different parts of the striatum (and of corresponding parts in other structures of the basal ganglia). The various components of the basal ganglia also have their corresponding cortical territories. The two together define various functional loops ("motor," "cognitive," and "limbic," or more detailed subdivisions) as defined by Alexander et al. (1986, 1990) and others. While most parts of the "motor" thalamus which receive input from the basal ganglia project to premotor, supplementary motor, and prefrontal cortex, these regions of the motor thalamus also send some projections to the primary motor cortex, and are presumably concerned with simple bodily movement, rather than more complex aspects of behavior and attention. The classic symptoms of both Parkinson's disease (rigidity, akinesia, tremor, as well as postural and gait disturbance) and Huntington's disease (chorea, athetosis, and ballismus) appear to be related to the lower levels of this hierarchy, the domain of actual bodily movement, of the limbs, or of the whole body.

Emphasis is usually placed on these classic symptoms because they are obvious on initial examination. The same pathological processes, operating in different parts of the striatum (or corresponding subdivisions of other nuclei of the basal ganglia), may produce a variety of symptoms in the behavioral and cognitive realms, but do not attract attention in the obvious way of major disturbances of bodily movement. Focusing just on the obvious "motor" symptoms may thus bias our understanding of the basal ganglia toward ideas of motor control and away from those of behavioral and attentional selection. If one defines diseases in terms of pathological processes rather than symptoms, there may thus be a sense in which "Parkinson's disease" (so-called) is just one among a variety of expressions of the basic pathological process underlying the disorder, seen only when it affects specific (i.e., "motor") parts of the striatum. A corresponding statement can be made about the classic motor symptoms of Huntington's disease.

A second general point is that, if the basal ganglia are concerned with behavioral selection, it is likely that this is expressed in part by accessing directly the mechanisms in the brain stem controlling automatically coordinated motor sequences such as gait, although (as already explained) other aspects of the selection process involve activation or suppression of activation of cell assemblies in the CTH network. In view of this, it would not be surprising if there were anatomical pathways from the basal ganglia to critical nuclei in the brain stem, which completely bypass the motor thalamus. Such pathways are well known. Details are given in Section 8.7.1, in the context of Parkinson's disease, to which these pathways have most direct relevance.

6.2 NEUROPATHOLOGY AND PATHOPHYSIOLOGY OF DISORDERS OF THE BASAL GANGLIA

The primary objective of Part II of this monograph, dealing with *disorders* of the basal ganglia, is to show how the symptoms of these disorders can be incorporated into the theory of basal ganglionic function, described in Part I, so far based mainly on evidence from the normal brain. As a start, it is necessary to summarize the basic neuropathological processes underlying some of the major disorders of the basal ganglia. Mainly, the essential pathology is degenerative cell loss of a variety of cell types, different for different disorders. Sometimes the cell loss forms the core pathology of a disorder and sometimes it may also represent a complication of other disorders, for instance, due to natural progression of the disorder or to failure to treat, or to excessive treatment. Cell loss, of whatever origin, may lead in turn to pathophysiological changes in otherwise intact neurons, consisting of increases or decreases of impulse traffic, and sometimes to changes in firing pattern. Some evidence of this sort has already been considered in developing the basic theory of operation of the basal ganglia. The subject is discussed in more detail below.

In the case of Huntington's disease, the basic pathology is massive degenerative cell loss. This occurs most prominently in the striatum affecting large numbers of its principal neurons (the medium spiny neurons). The pathology may be so severe that there is obvious macroscopic shrinkage of the striatum in advanced stages of the disease when studied postmortem. Cell loss may also occur in other parts of the forebrain (e.g., the cerebral cortex). Correspondingly, Huntington's disease, in addition to its characteristic "motor" symptoms, may include cognitive symptoms, some of them akin to psychosis (Bruyn, 1968), others to dementia.

In the case of Parkinson's disease, the basic pathology is more restricted degenerative cell loss, mainly of pigmented (melanized) brain-stem neurons using catecholamines as neurotransmitters. Midbrain neurons in the substantia nigra (pars compacta), which provide the dopaminergic projection to the striatum (and other parts of the basal ganglia), are prominent targets of this degenerative process. The classic symptoms are known to appear when dopamine depletion in a specific part of the striatum—the putamen—reaches a severe degree (Kish et al., 1988). However, as shown by Kish et al. (1988), the pathological basis of Parkinson's disease—loss of the dopaminergic nigrostriatal projections—can affect not only the putamen, but also all parts of the striatum including the caudate nucleus, likely to be involved in behavioral planning and attentional selection. There are other potential regions of

cell loss in Parkinsons's disease. The abnormal "Lewy bodies" are found in neurons of many brain-stem nuclei (not only monoaminergic ones), but it is not clear whether this is in itself harmful or merely a side effect of other pathological processes (Jellinger, 1999). Cell loss does, however, occur sometimes in noncatecholaminergic nuclei including the pedunculopontine nucleus (see Section 8.7.2).

An important innovation in the following account of disorders of the basal ganglia is the inclusion of dopamine-mediated states of psychosis. There is a risk of creating confusion here, because such psychotic states occur in a variety of circumstances and notably in the complex disorder called schizophrenia. Some researchers hold that the terms schizophrenia and psychosis are equivalent in meaning. This is not the belief of the present author and no attempt is made here to give an account of the pathophysiology of schizophrenia *per se*. However, to forestall criticism, it should be made clear that the author believes that two nearly separate bodies of theory are needed to understand schizophrenia: The theory of dopamine-mediated psychotic states and the theory of the underlying and enduring traits, which form the core of schizophrenia. The latter body of theory is based on abnormalities outside the basal ganglia, not primarily involving cell loss, while the theory of psychosis is based on evidence for overactivity of transmitter dopamine in the striatum. One of the deeper questions about schizophrenia is then to elucidate the relation between the enduring traits, which form its core and the transient destabilization of dopamine release, which leads to psychosis. This question will not be answered in the present monograph, which has more limited objectives. As far as psychosis is concerned these objectives are to explain how, in the context of the theory of the basal ganglia expounded above, overactivity of nigrostriatal dopamine neurons (known to occur in psychotic states) can lead to the symptoms of psychosis.

The final class of disorders of the basal ganglia to be discussed here involves three apparently disparate syndromes. These are (i) Tardive dyskinesia (a late consequence of prolonged high-dose neuroleptic therapy in some cases, although a similar syndrome sometimes occurs in other circumstances); (ii) Peak-dose dyskinesia seen sometimes in advanced cases of Parkinson's disease during L-DOPA therapy; and (iii) Neuroleptic-induced supersensitivity psychosis first described by Chouinard et al. (1978), and some similar instances of neuroleptic-refractory psychosis of other origins. It has already been suggested (Miller and Chouinard, 1993) that these three syndromes have a common pathological basis, namely, the loss or damage of cholinergic interneurons, which form a small proportion of striatal cells. The decisive evidence for these postulates is not yet available, although some evidence supporting the postulate has appeared since 1993. Here, in the context of the overall theory for the basal ganglia, it is possible to extend the theory on which this postulate was based beyond the 1993 paper, especially in the fields of phenomenology and neuropharmacology.

In Section 2.2, it was explained that, alongside the subdivision of the basal ganglia into a variety of nuclei, each nucleus also can be divided into territories, such that connected territories in each nucleus define functional circuits ("sensorimotor," "associative," "limbic," etc.). This demarcation is based mainly on connectional anatomy. However, Grabli et al. (2004), investigated it in terms of function using the method referred to in Section 3.4.3.2, in which bicuculline was microinjected into

GPe in monkeys to block inhibitory transmission from the striatal input. As described in that section, abnormal movements contralateral to the injection site were produced after injection into the sensorimotor parts of GPe. These movements persisted when the animal performed a task involving spatially selective responding, and could therefore be designated as genuinely "involuntary." However, similar injections into the associative parts of GPe led to general hyperactivity with disruption of the spatial task (involving retrieval of a food reward hidden in each of the 18 wells). This was interpreted as a disruption of focused attention. Injections into the limbic region of GPe led to a different behavioral abnormality, namely persistent repetition of fragments of behavior, which were parts of the animal's normal repertoire, though not normally performed repetitively. This behavior ceased when the animal performed the spatial task, and was thus similar to human "voluntary" behavior. It was termed "stereotypy," because of its similarity to stereotypy seen after stimulant injection (see Section 3.4.4.4) or after prolonged confinement in environments allowing limited free movement (Bryant et al., 1988; Ridley, 1994). In contrast to injections in the sensorimotor region, neither of these two behavioral syndromes involves abnormalities in movement *per se*. In rats, the pallidum (=GPe) is too small to replicate such experiments. However, local injections of dopamine agonists into the striatum, a larger structure, also give an indication of how different functions are related to different territories in this complex nucleus (Miller and Beninger, 1991; Dickson et al., 1994). Limb or oro-facial movements are represented in the lateral aspect of the striatum (limbs dorsal to the oro-facial region), while whole-body movements are represented more medially near the lateral ventricle. The exact significance of different motor/behavioral effects in terms of functional circuits through the basal ganglia is not well resolved in rat. For instance, both oral stereotypy produced by stimulants and "vacuous chewing" occurring as a consequence of prolonged neuroleptic administration have been attributed to the same (ventrolateral) striatal region (Dickson et al., 1994; Grimm et al., 2001). The relation of these two and the extent to which either reflects a disturbance of coordinated oro-facial movements, as opposed to stereotyped repetition of well-coordinated programs of behavior, is not clear.

The significance of such experiments for disorders of the basal ganglia in humans is that these disorders, in different circumstances, may produce symptoms in a variety of functional domains. In moving from experimental animals to humans, one has to extend the functional domains as defined in monkeys to include psychomotor and cognitive performance distinctive of humans. Given this, the symptoms arising in the basal ganglia are sometimes clearly in the domain of isolated movements ("microbehavior"), sometimes in that of larger-scale behavior, sometimes in the realm of attentional focus in defined tasks, and sometimes revealed as abnormal symptoms in the realm of thoughts and beliefs. In the following chapters, each of these types of symptom will be described and suggestions made for the functional domain of which each symptom class is a manifestation. In Chapter 11, the different symptoms of various disorders of the basal ganglia are tabulated to show parallels between symptoms in different domains, produced by similar pathological processes but expressed via different circuits.

Some of the evidence needed to support the explanatory arguments linking basic pathology or pathophysiology to phenomenology of abnormal movement (and other symptoms) is not easily obtained from "objective" accounts in textbooks or research papers. It is sometimes necessary to get closer insight into the actual subjective experience of patients who have these symptoms. In this regard, the narrative approach adopted by Oliver Sacks is sometimes used. Thus, some theoretical points (especially about Parkinson's disease and dyskinesias) are substantiated by detailed quotations from his book *Awakenings*. Likewise, in developing the theory of psychosis, some points are supported by first-person accounts of psychotic illness. As a scientist without clinical training, these are the best sources I can find to elucidate some key points in the argument.

7 Huntington's Disease

In developing arguments for the basic theory of the basal ganglia, reference has already been made to Huntington's disease. The differential loss of striatal neurons of origin of the indirect versus direct pathways, leading respectively to hyper- versus hypokinetic symptoms, was important evidence contributing to the postulated opposite behavioral roles of those two pathways through the basal ganglia. Here, some further discussion is added on to the details of motor and other phenomenology of the disorder.

The cell loss of the principal neurons of the striatum does not affect the dopaminergic reinforcing input, which mediates synaptic strengthening and behavior modification. There is also no pathological exaggeration of the dopamine-mediated modification process by which purposeful voluntary action is acquired. Therefore, one would expect a loss of behavioral repertoire there, rather than a loss of the processes of modification of behavior, as occurs in some other disorders considered below. Most obvious are the "positive" motor symptoms, such as chorea, athetosis, and ballismus, reflecting the loss of ability to inhibit unwanted movement, as a result of loss of neurons of origin of the indirect pathway. Less obvious, but well documented in advanced cases is the "negative" motor symptom, namely akinesia, in which loss of neurons of origin of the direct pathway dominate the picture.

If there is a haphazard loss of neurons by which extraneous action could be suppressed, one would expect the motor pathology which emerges to be the release of genuinely purposeless acts, rather than a distortion or exaggeration of normal purposeful routines. Descriptions of chorea and athetosis fit this expectation: Chorea is described as ceaseless complex jerky movements of the limbs and athetosis as ceaseless writhing movements of the hands (Dorland's Illustrated Medical Dictionary, 30th Edition, 2003). However, the same syndrome can affect any part of the motor apparatus. The definition of chorea given by the World Federation of Neurology (Lakke, 1981) is "a state of excessive spontaneous movements, irregularly timed, randomly distributed and abrupt." The abnormal movements may cause an inability to maintain a constant level of postural tone (e.g., when the tongue is protruded or during a handgrip [Caviness, 2000]). Other accounts indicate that a pseudopurposive appearance may be present, for instance, as an exaggeration of gesture, where patients incorporate involuntary choreiform movements into apparently purposeful gestures or convert an initial involuntary movement into a voluntary one (Caviness, 2000; Marshall, 2004). However, there is no suggestion that these movements in themselves are fragments of purposeful movement, as appears to be the case for tics (see Section 10.3). Unlike tics, chorea is not stereotyped and repetitive (Folstein, 1990). These descriptions fit the notion that the movements are an abnormal reflection of the ever-changing neuronal activity relayed from cortex to basal ganglia. Normally, such movements are suppressed (hypothetically by activation of neurons of the indirect pathway), so that truly purposeful acts can be emitted undisturbed by such

extraneous activity. This perspective also fits the fact that the movements are worsened by emotional or other stress, which, plausibly, is accompanied by an increase of such extraneous activity, afferent to the basal ganglia (Folstein, 1990; Kremer, 2002). The movements cease during deep sleep (Quarrell and Harper, 1991). This could be a consequence of the fact that, in deep sleep, the intricate coordination of activity of the cortex for purposes of information processing is replaced by large coherent electrographic waves. These would activate striatal cells *en masse*, and the local inhibition ("activity control") of the medium spiny neurons that remain intact would cancel out activity in any cell group, which might release specific movements.

These movements are usually completely involuntary (unlike some other symptoms of disorders of the basal ganglia, where subjectively there may be a growing "urge" to move, which can be resisted for a while, but which builds up until the movement "bursts forth"). Indeed, mild and intermittent choreic movements seem not to be noticed by many patients (Kremer, 2002). Automaticity of movement is not in itself pathological, since many movements (blinking, swallowing, arm swinging during walking) are automatic and involuntary. However, unlike these, choreiform movements cannot be voluntarily suppressed. They are continuously present during waking hours. In the early stages of the disease, voluntary action or mental concentration can reduce the movements (Quarrell and Harper, 1991), but this is no longer possible as the disease advances. Presumably, this effect occurs because a specific voluntary act involves vigorous activity in a few striatal neurons, which, by local inhibition in the striatum (referred to above as "activity control"), reduces overall levels of other concurrent activity. This would require a degree of overall integrity of the striatal mechanisms, which explains why the effect of voluntary activity or mental concentration to limit choreic movements is seen mainly in the early stages of Huntington's disease.

Choreiform movements in themselves are said to be well coordinated (Dorland's Illustrated Medical Dictionary, 30th Edition, 2003), and thus presumably depend on abnormality above the level (brainstem, cerebellum, and spinal cord) at which automatic and reflex motor coordination is organized. Balance of the whole body is remarkably well maintained, and, during gait, the angle of the ankle at the moment of heel-strike is not more variable than in normal subjects, despite increased variability during the swing phase (Reynolds et al., 1999). Mobility for everyday activities is surprisingly well maintained despite conspicuously abnormal movements (Quarrell and Harper, 1991). This is to be expected, given that in the hyperkinetic stages of the disease, the direct pathway is not severely affected, so that voluntary and purposeful active movements are not prevented (albeit mixed with involuntary abnormal ones). Nevertheless, it has been observed (Wilson, 1925) that all sorts of abnormal combinations of agonist and antagonist activities may occur (see also Thompson et al., 1988). Although Wilson suggested that in this disease Sherrington's law of reciprocal innervation no longer holds, there is not a systematic cocontraction of agonist and antagonist. It was noted above that (micro)behavior may be expressed by activity at a single muscle. Thus, it is still possible to maintain that these abnormal combinations of muscle activity are pathologies of voluntary behavior, rather than that of the more stereotyped aspects of motor coordination in a strict sense.

The symptom of ballismus deserves special comment. Classically, it has been regarded as a symptom resulting from lesions of the subthalamus (usually unilaterally, when *hemi*ballismus is observed). However, that is a relatively rare cause. There is a wide variety of other causes including Huntington's disease (Vidakovic et al., 1994), where it has been described as the most severe manifestation of chorea (Kremer, 2002). The symptom involves sudden whole-limb movements initiated from the proximal limb muscles (Dorland's Illustrated Medical Dictionary, 30th Edition, 2003). In normal circumstances, these muscles (e.g., the "rotator cuff" muscles of the shoulder joint) act as fixators holding the proximal joint fixed as a steady base, so that more delicate active movements can be made effectively with the more distal parts of the upper limb. Thus, ballismus can be regarded as a specific release phenomenon, the failure to suppress aspects of movement, which are normally suppressed as a component of a pattern of instrumental behavior.

The symptoms of Huntington's disease are not limited to choreo-athetosis and ballismus. As the disease progresses, akinesia as well as rigidity and dystonia develop (Wilson, 1925; Thompson et al., 1988; Quarrell and Harper, 1991; Biglan and Shoulson, 2003). Akinesia, as explained in Section 3.4.3.3 is a likely consequence of loss of neurons of the direct pathway from the striatum. Rigidity and dystonia are more difficult to understand. These symptoms appear to be genuinely those of motor coordination rather than behavioral selection. The theoretical basis of rigidity, which is complex, is discussed later (Section 8.7.3) in the context of Parkinson's disease. Dystonia occurs in a wide variety of conditions, including those whose pathology can be defined as well as others where it cannot yet be. It presents a number of paradoxical features, which are considered briefly in Section 10.6.1 of Chapter 10.

Following the insight that there are several parallel functional circuits through the basal ganglia, one would also expect that symptoms in Huntington's disease should include not only "motor" manifestations (i.e., microbehavior), but also macrobehavioral, cognitive, and psychiatric symptoms. Cognitive and psychiatric symptoms in Huntington's disease, which are many and varied, are well documented (Craufurd and Snowden, 2002). In the cognitive realm, they include impairments in executive function and memory. Psychiatric aspects involve affective symptoms (mainly depression) and isolated psychotic symptoms, but these rarely fulfill the criteria for formal diagnosis of disorders in the schizophrenia spectrum, even when the exclusion criterion of "identified organic causes" for the disorder is waived. (In earlier decades, there was often an initial misdiagnosis of schizophrenia, later revised to Huntington's disease. This is less common when modern criteria for psychiatric diagnosis are used.) In view of there being cell loss in the cortex as well as in the striatum in Huntington's disease, it is difficult to give a precise interpretation of most of the above changes in terms of the theory of the basal ganglia presented here. However, one aspect of the abnormal psychological function in Huntington's disease is "irritability": The slightest provocation may provoke an outburst of angry or violent behavior. In some cases, to quote Craufurd and Snowden (2002), "the patients themselves will complain that they have become subject to sudden and uncharacteristic upsurges of anger that often surprise them by their ferocity and lack of warning, but subside equally quickly, leaving the individuals shaken and filled with remorse." This description betrays an involuntary release of behavior or

of strong emotions governing behavior, which are normally suppressed. As such, this symptom is parallel at the level of large-scale behavior to the release of motor acts, which are usually suppressed, as is found (for instance) in ballismus.

In neuropathological terms, cell loss in the striatum occurs preferentially in the dorsal caudate and putamen, rather than in the ventral putamen and nucleus accumbens (Roos et al., 1985; von Sattel et al., 1985; Ferrante et al., 1986). There is little evidence to allow correlation between striatal regions, where cell loss is most prominent and the nature of the resulting symptoms ("motor," behavioral, or psychiatric). However, Starkstein et al. (1988) reported that caudate atrophy correlated with oculomotor dysfunction and cognitive decline, but not with chorea (presumably, a reflection of cell loss in the "motor" regions, i.e., the putamen). Peinemann et al. (2005) found that gray matter loss in the caudate correlated with impairments in cognitive ("executive") functions in the early stages of Huntington's disease, although cortical tissue loss in the region of the insula also showed such correlation.

It is common for choreic and other hyperkinetic patients to be treated with neuroleptic drugs. Likewise, the symptom of behavioral irritability in Huntington's disease can be treated with such medications. In either case, the benefit is offset by sedation and extrapyramidal side effects (dystonia, parkinsonism, and akathisia) to be expected from such treatment (Morris and Tyler, 1991; Craufurd and Snowden, 2002). The basis of the beneficial effects in the theory of the basal ganglia presented here is mentioned in Section 8.2, after dealing with pathophysiological findings in Parkinson's disease.

In the next chapter, dealing with Parkinson's disease, an important issue is whether symptoms originating in the basal ganglia are expressed via thalamocortical pathways or via direct relay to brain-stem nuclei. One source of evidence to answer these questions is the effectiveness of the neurosurgical approach called thalamotomy to alleviate symptoms. For Huntington's disease, however, there is little evidence on this approach to treatment. Stereotactic surgery has little role in treatment, since any minor improvement it produces is of little significance in the overall clinical picture and course of the disorder (Narabayashi et al., 1973). It is therefore, not at present possible to determine whether cortical or subcortical pathways are more important in the expression of the hyper- and hypokinetic symptoms of this disorder.

8 Parkinson's Disease and Parkinsonian Syndromes

8.1 INTRODUCTION

Parkinson's disease is a complex disorder, with a wide variety of symptoms, even before the complications of the advanced disease set in. Much discussion is needed to encompass all this phenomenology within the theory developed in Part I. The cardinal symptoms of the disease are commonly said to be tremor, rigidity, and akinesia. However, there are many other symptoms, including disturbance of gait and posture, as well as cognitive impairment. The different symptoms do not vary in parallel as the disease progresses. Thus several papers have suggested that there may be two subtypes, one dominated by tremor independent of other motor symptoms and with little intellectual decline, the other, which was generally more severe, dominated by akinesia, rigidity, postural and gait problems, and cognitive impairment (Mortimer et al., 1982; Zetusky et al., 1985; Jankovic et al., 1990). Evidence, such as it is, implying that these two subtypes reflect dopamine depletion in different parts of the striatum (different functional circuits) is mentioned in the relevant sections below. Another neuroanatomical issue is whether symptoms are expressed via the thalamo-cortical output from the basal ganglia or by descending pathways direct to brain-stem nuclei. In the sections below, abnormalities dependent on the thalamo-cortical outflow (cognitive/attentional impairments and tremor) are discussed first (Sections 8.3 through 8.6) followed by discussion of those involving relay direct to the brain-stem (akinesia and rigidity dealt with in Section 8.7). Of the cardinal symptoms, rigidity, tremor, and perhaps akinesia appear to be abnormalities of motor coordination, rather than of behavioral selection. If so, this is a major challenge for the theory presented here. However, before discussing them, the question should be asked whether these are really the essential core features of the disorder. Hints were made in Section 3.4.5 that it might not be so.

8.2 THE "GOAD AND THE HALTER" IN PARKINSON'S DISEASE

Oliver Sacks is of the clear opinion that the above-mentioned symptoms are not the core features of Parkinson's disease. In the introduction to "*Awakenings*," he mentions that the very first qualities of Parkinson's disease to be described were *festination* and *pulsion*. In objective terms these consist of hurried movements (e.g., of gait or in writing), although the hurried movements may become smaller and smaller in amplitude and so come to an uncontrolled halt. Subjectively they are often accompanied by a sense of motor urgency and impatience. Sacks quotes Charcot's

phrase—"cruel restlessness"—to describe Parkinson's disease. Of a similar nature is the symptom of *akathisia*, more commonly seen in psychiatric patients as an unpleasant side effect of treatment with neuroleptic drugs. This is manifested objectively as excessive restlessness and "fidgetiness," often accompanied by a subjective sense of restlessness. These symptoms represent release of large-scale behavior, rather than of simple motor responses.

Opposed to this is the experience of active retardation or resistance to movement and speech (or even thought). This is the more familiar side of Parkinson's disease, sometimes identified as akinesia. However, the active retardation of movement becomes part of an endless unresolved conflict with the more active symptoms. To quote Sacks:

> Patients so affected find that as soon as they "will" or intend or attempt a movement, a "counter will" or "resistance" rises up to meet them…. force against counter force, will against counter will, command against countermand. (Copyright 1973 by Oliver Sacks, with permission of the Wiley Agency.)

Between these two, in the words of Charcot "there is no truce." The two sides of parkinsonism occur not only in the domain of movements and behavior, but also in that of thoughts. For instance, one of Sacks' patients describes how, long after the acute affliction with encephalitis, but prior to L-DOPA therapy:

> thoughts would dart into my mind, not my own, not intended

and also

> thoughts would suddenly vanish, smack in the middle of a sentence sometimes … They'd drop out, leaving a space, like a frame minus a picture. (Robert, O. in "*Awakenings*"; Copyright 1973 by Oliver Sacks, with permission of the Wiley Agency.)

One of Sacks' patients describes this unresolved conflict as "the goad and the halter." Akinesia is then neither an idle nor a restful state, but the result of "mighty and equal antagonisms." This appears to be what is fundamental to Parkinson's disease—not rigidity and tremor. In fact one of Sack's patients says explicitly:

> I have various banal symptoms which you can see for yourself. But my *essential* symptom is that I cannot start and I cannot stop. Either I am held still, or I am forced to accelerate. I no longer seem to have any in-between states. (Copyright 1973 by Oliver Sacks, with permission of the Wiley Agency.)

These symptoms are clearly not disorders of motor coordination. They seem to be pathologies of intentional, purposeful, voluntary behavior (including thoughts) rather than abnormal involuntary and purposeless motor phenomena. The impairment in suppression of behavior has been documented in a more controlled situation (Gauggel et al., 2004), where patients made a continuous series of choice reaction time (RT) responses, interspersed on 25% of trials by a "stop" signal. The time advance of the stop signal with respect to the subsequent trigger for the RT response sufficient to

permit response inhibition on 50% of trials was determined. This was found to be 70 ms longer in Parkinson's disease patients than in control subjects, although the RT in the primary task did not differ between groups. In other words, a "NoGo" command could not be initiated so rapidly as in normal subjects. It would be of interest to know if this impairment correlated with clinical signs such as akathisia or festination.

How are we to understand these pathologies of voluntary behavior in the context of the present theory? In Section 2.6, arguments were presented, based on electrophysiological studies in normal animals, that only a few striatal cells become active at once. In normal animals, most striatal cells are nearly silent, and only a small fraction show higher rates of firing (Schultz and Ungerstedt, 1978; Orr et al., 1986; Sandstrom and Rebec, 2003). As a result, according to the theory, only one piece of behavior is emitted at once. From the reasoning about "activity control," it follows that it is unlikely that there be coactivation of signals for both activation and suppression of the same behavior, although these two may simultaneously affect *different* parts of the motor apparatus (e.g., active hand movements combined with fixation of the shoulder joint).

The situation is very different in Parkinson's disease. In animal models of parkinsonism, such as rats treated acutely with a neuroleptic drug or when dopamine innervation is destroyed in rats with 6-hydroxydopamine or in monkeys with MPTP, there is strong evidence for elevation of firing in very many striatal neurons (see Section 3.4.5). Not all the published studies show elevation, which is statistically significant, perhaps because dopamine depletion is not necessarily complete in the region studied. The study of Orr et al. (1986) is the most informative. Their cumulative frequency histograms of spontaneous firing frequency (Figure 8.1) show, in vehicle-treated rats, that only 2–3% of cells had firing rates above 0.1/s. In rats with the most severe dopamine depletion, over 40% of cells had firing rates above 0.1/s, and 20% had rates above 1/s. This study (like that of Schultz and Ungerstedt, 1978) was conducted in anesthetized preparations. In free-moving preparations, firing rates are higher, but the differential between normal and parkinsonian states is still present (see Section 3.4.5). Electrophysiological evidence on unit firing rates cannot determine how the cells with increased firing rates are distributed among neurons of origin of the direct versus the indirect pathways. However, evidence from correlation of unit firing rates with parkinsonian impairments in rats and from studies of microinjection of drugs blocking or activating inhibitory or excitatory transmitter receptors in the striatum (or other nuclei) makes it plausible that the increase in firing applies to neurons of origin of both the direct and indirect pathways (see discussion in Section 3.4.5).

This evidence makes it very plausible to assume that the neurons activated in low-dopamine states are a random sample of those from which both the direct and indirect pathways originate. In the illustrations of Filion and Tremblay (1991) GPe neurons in parkinsonian monkeys show decrease in firing, largely due to identifiable periods of inhibition. GPi neurons showed increased firing. The monkeys in this study were hypokinetic or akinetic. There are no studies reporting on unit firing in relation to symptoms such as festination or akathisia, and the literature on neuroleptic-induced akathisia in animals is very small. In humans, the incidence

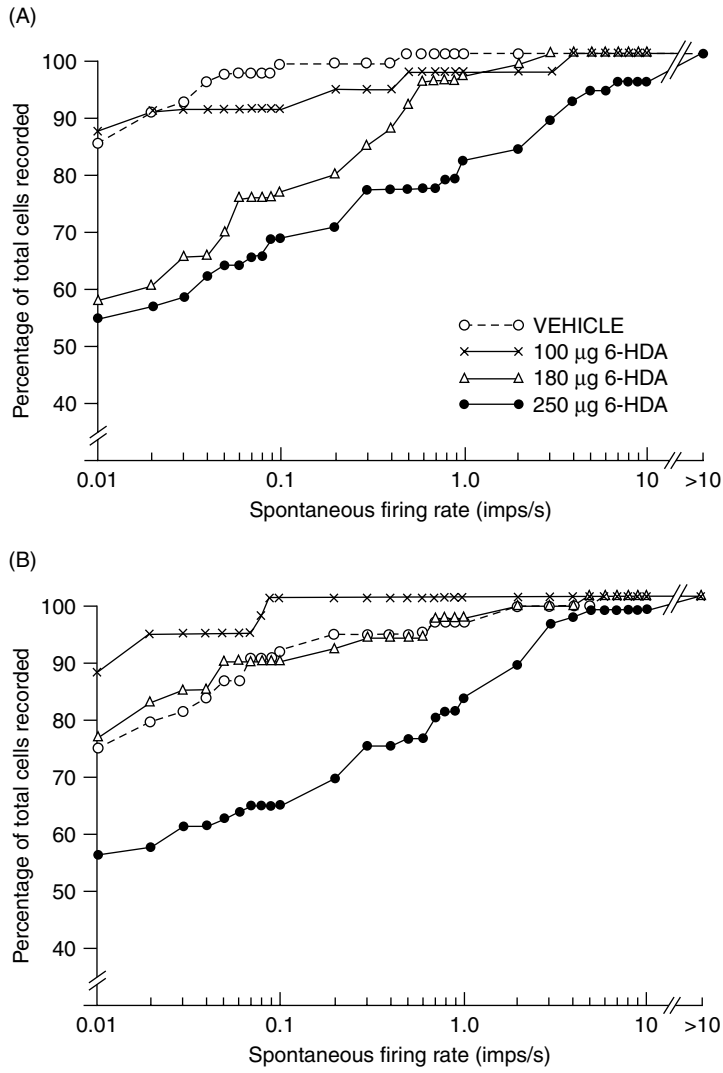

FIGURE 8.1 Cumulative frequency histograms of spontaneous firing frequency in medial (A) and lateral (B) striatal neurons of rats with various degrees of dopamine depletion (vehicle and three doses of 6-HD administered intraventricularly). Each point on a curve indicates the percentage of total neurons with firing rate equal or less than the value shown on the *x*-axis. (Reprinted from Orr, W., Gardiner, T.W., Stricker, E.M., Zigmond, M.J., and Berger, T.W. *Brain Res.*, 376, 20–28, 1986. Copyright [1986], with permission from Elsevier.)

of drug-induced akathisia is related to the D2-blocking potency of the neuroleptic drug, rather than the affinity at other receptor sites (Sekine et al., 1999). Assuming there is overactivity in neurons of origin of both the direct and the indirect pathways, one would then *expect* the perpetual strife, described by Sacks and others, between the urge to do something and the urge to restrain from doing it—the "goad and the

halter." Festination—a hurried gait, transforming into frozen posture—captures both aspects of this. The fact that these symptoms of Parkinson's disease—festination or akathisia—refer to activity *in general*, or inability to start moving *in general*, rather than exaggerations of *specific* actions or suppressions of *specific* actions fits well the physiological finding that there is widespread overactivity of striatal principal cells. From this argument, it might also be expected that the urge "to do" and to "stop doing" could occur even at the same time, rather than in reciprocal relation to each other. In other words, the "goad" and the "halter" are not mutually exclusive.

At the end of Chapter 7, reference was made to the fact that neuroleptic drugs are one of the treatments preferred for control of the abnormal movements and impulsive behavioral release of Huntington's disease. From the mechanism just explained, we can now see a theoretical rationale for this: If neuroleptic drugs cause a widespread increase in activity in striatal medium spiny neurons, this will include the neurons of origin of the indirect pathway (even though the partial loss of these is hypothetically the cause of the abnormal movements). Such increase of activity would mean that effective suppression of extraneous activity could occur even if the number of functional neurons of this class was reduced. At the same time, increase in activity in this pathway could also lead to the parkinsonian motor side effects more commonly associated with such medications, and also seen when used to treat Huntington's disease.

The actual cause of the increase in firing in low-dopamine states is not fully understood. It is widely held that dopamine has inhibitory effects overall in the striatum, such that dopamine depletion would lead to an increase in activity. However, the full explanation of the increase in firing is undoubtedly more complex, involving diverse biophysical changes in striatal neurons, as discussed by Tseng et al. (2001a). One component has recently been revealed by Shen et al. (2005). A potassium current in medium spiny neurons is opened as voltages rise toward and above threshold, thus forming a sensitive control of firing rate. Acetylcholine, acting via muscarinic receptors closes the channels for this current, thus raising membrane potential and increasing firing rate. The specific muscarinic receptor involved is the M1 receptor, which is present in almost all medium spiny neurons, regardless of whether they are part of the direct or the indirect pathway (Yan et al., 2001). It is well known that dopamine, via D2 receptors, inhibits the firing of striatal cholinergic neurons, thereby reducing acetylcholine release (see also Section 9.5). Thus, blockade of D2 receptors, or dopamine denervation in the striatum increases ACh release from these interneurons, and this leads to increase in firing rate of medium spiny projection neurons. The wider significance of this may be evident more at times of increased dopamine activity: Concomitant with dopaminergic reinforcement of selected excitatory synapses, there should be an overall reduction of excitability. Together these effects ensure high signal-to-noise ratio, so that the effects of the reinforced synapses "stand out" from a generally low level of impulse traffic. There are also additional unresolved complexities in the action of dopamine on medium spiny neurons: D2 receptors act directly on these neurons to reduce firing (Hernandez-Lopez et al., 2000), and D1 receptors also have direct biophysical effects in addition to those which mediate strengthening of excitatory synapses (Surmeier et al., 1996b). Moreover, it is not resolved whether the increased firing of striatal neurons in

low-dopamine states is an acute effect of the low-dopamine tone or requires extended time in this state for it to develop. The evidence cited above refers to chronic low-dopamine states produced by dopamine denervation. It is unclear whether the same elevation of firing rates is produced by acute blockade of dopamine receptors with neuroleptic drugs (see Section 3.4.5).

8.3 COACTIVATION OF STRIATAL NEURONS AND COGNITIVE PROBLEMS ASSOCIATED WITH PARKINSONIAN SYNDROMES

The previous subsection showed how, in parkinsonian syndromes, there is a *general* excess of striatal neural activity, driving both activation and suppression of behavior. In more detail, however, there is also evidence of a breakdown of the process by which one strategy of behavior or one focus of attention is selected to the exclusion of others. The mechanisms by which such selection normally occurs were discussed in Part I. It was apparent that one of the most sophisticated pieces of neural design in the basal ganglia is that needed to solve the "credit assignment problem." In other words it is necessary to ensure that the patterns of activity relayed from the cortex, which the striato-nigral system detects as being motivationally favorable or unfavorable, can address each behavior-related cell assembly of the CTH network specifically, and exclusively, that is, without the extensive divergence which occurs in the cortex and some other neural networks. This highly specialized combination of morphology and physiology appears to be a vulnerable point in the basal ganglia, breakdown of which, in parkinsonian syndromes, leads to impairment due to loss of the specificity in the use of the "alternative labeled line" pattern of connectivity. The present subsection discusses evidence on this, documenting cognitive deficits arising from loss of the specificity of targeting of cell assemblies by the basal ganglia ("coactivation").

It was argued in Section 2.6 that, in the normal situation, any activity in striatal cells generates, via collateral inhibition, an inhibitory tone within the striatum, which prevents an excessive number of cells being activated at one time. As a result, the distribution of firing rates across striatal neurons in the normal state is highly skewed, with many neurons almost silent, and a few with higher firing rates (Section 3.4.5; see Figure 8.2). After dopamine depletion, overall firing rates increase, and there is a lower proportion of near-silent neurons (Schultz and Ungerstedt, 1978; Orr et al., 1986). In other words coactivation of many more striatal neurons can occur in the dopamine-depleted striatum than in the normal one. A similar conclusion can be drawn from considering the capacity of the striatum to transmit electrographic rhythms. Striatal medium spiny cells do not generally transmit electrographic rhythms from the cortex to other structures of the basal ganglia, though cortical rhythms may transmit to an extent sufficient to form subthreshold rhythms in membrane potentials (Charpier et al., 1999). In parkinsonian syndromes this changes according to Tseng et al. (2001a). These authors show, by simultaneous recordings of cortical EEG and medium spiny cell membrane potentials in urethane-anesthetized rats, that the dopaminergic lesion makes cortical slow waves (prominent in this preparation at 0.4–2 Hz) transmit to the striatal cells sufficiently strongly to be expressed in their firing. Cortical oscillations thus come to be reflected in spike trains of 60% of neurons. Normally, this does

not happen because firing rate is too slow to be a reflection of membrane potential changes. This is another indication that there is likely to be a considerable degree of coactivation of neighboring medium spiny cells, not found before the dopaminergic denervation.

These results can be taken as an evidence that the mechanism of collateral inhibition in the striatum may not be strong enough to impose strict limits on the number of active striatal cells in the circumstances of parkinsonian syndromes. Exactly why "activity control" is no longer effective is not clear. One possibility is that an indirect effect of dopamine depletion is to weaken the already-weak collateral inhibitory influence. Whatever the cause, the implication for the globus pallidus and SNR is that inhibition from striatal cells may, more commonly than normally, influence neurons along many channels simultaneously. If, in Parkinson's disease or subclinical versions of it, multiple coactivation, rather than activation of just a few labeled lines tends to prevail in the basal ganglia, it has implications for the selectivity with which activity can be released in single cell assemblies in the CTH network. It is expected that it would become more difficult for activity in cortical cell assemblies to be kept separate. Several predictions can then be made for psychological experiments in parkinsonian syndromes. (i) There should be impairment in selective focus of attention, with greater influence of distracter stimuli. (ii) There should be impairment in discrimination tasks. (iii) There should be impairment beyond that in normal subjects during dual-task performance. (iv) Conversely, mental association should occur more readily than in normal subjects.

There is evidence supporting each of these predictions: With regard to focus of attention, Sharpe (1990, 1992) used a dichotic monitoring task with subjects required to press one of two buttons, and with attention focused on either left or right ear. Early Parkinson's disease patients had more difficulty than normal subjects in ignoring the irrelevant stimulus in the nonattended ear. In a selective attention task in the visual sense (Lee et al., 1999), no impairment in focus was found in parkinsonian patients. However, in another visual task (Filoteo et al., 2005), where stimuli varied on four dimensions, and categorization was based on only one dimension, parkinsonian patients were impaired by the irrelevant dimensions, especially when their number increased. An electrographic manifestation of the impairment in the auditory sense was shown by Vieregge et al. (1994): The "processing negativity," that is, the amplitude difference between potentials produced by attended and unattended tones was smaller than normal in parkinsonian patients (especially from 200 to 300 ms after the stimulus onset).

With regard to discrimination learning, Channon et al. (1993) found impairment in parkinsonian patients in more complex problems. Joosten et al. (1995) found, for a variety of discrimination problems, that parkinsonian patients needed more trials than normal subjects. A study of somatosensory discrimination (Weder et al., 1998) found that parkinsonian patients were significantly worse than age-matched normal subjects. In the visual sense, discrimination was reported not to be impaired in Parkinson's disease (Schneider and Pope-Coleman, 1995) or only marginally so (Russ and Seger, 1995). However, in a test of visual discrimination of superimposed images, impairment was found (Katsarou et al., 1998). In other visual discrimination tasks, with two dimensions present, only one of which was

relevant (Maddox et al., 2005), parkinsonian patients could select the right rule for discrimination, but were impaired because they used broader category boundaries. Shin et al. (2005) required subjects to discriminate the orientation of gratings and found the threshold difference in orientation to be higher in parkinsonian patients than normal subjects, especially if the former were unmedicated. In another category-learning task (Shohamy et al., 2004), combinations of cards were presented which allowed subjects to work out the correct response. Different cards were associated at different probabilities with the correct response. Control subjects could work out the optimal response, based on combining the predictive value of different cards. In parkinsonian patients, this strategy was never reached and performance was based on the predictive value of just a single card. In other words, the finer discrimination based on combinations could not be acquired.

In dual-task performance, several studies have shown parkinsonian patients to be impaired (Brown and Marsden, 1991; Dalrymple-Alford et al., 1994; Ho et al., 2002; Marchese et al., 2003; Kemps et al., 2005). In these studies, in Parkinson's disease patients, concurrent tasks interfere with pursuit tracking, speech or postural stability, tapping targets in a defined sequence, or tone monitoring. They also increase the variability in timing of the phases of gait (Yogev et al., 2005). In terms of attentional theory, parkinsonian subjects exhibit a reduction in "processing resources."

With regard to the facility for mental association, Spicer et al. (1994) used a lexical decision task, with primes semantically related, or not related, to the target, using RT as the response measure. Parkinsonian patients, though slower than normal controls, showed greater than normal facilitation by semantically related primes.

As a whole, the evidence is compatible with the hypothesis that (apart from major motor symptoms), there is, in Parkinson's disease, a tendency to coactivation of cell assemblies, rather than selective release of individual assemblies. This conclusion from psychological evidence has its counterpart based on biological evidence, using electrophysiological methods of recording or stimulation. These include both transcranial magnetic stimulation (TMS) of the cortex, and recording cortical activity in the form of EEG or event-related potentials (ERPs). Using TMS, single pulses applied over the motor cortical area produce a brief phase of EMG activation followed by silencing of spontaneous EMG activity (Calancie et al., 1987; Holmgren et al., 1990). This silencing is indicative of inhibition that could, in principle, be occurring at either the cortical level or at the level of the spinal motoneurons. The part played by inhibition at the latter site can be assessed independently by delivering stimuli to peripheral nerves with monitoring of postexcitation pauses in EMG activity. In Parkinson's disease, the silent period after TMS is shorter than normal (Cantello et al., 1991; Priori et al., 1994; Berardelli et al., 1996), while the silent period after peripheral nerve stimulation is actually lengthened. When Parkinson's disease is unilateral, the shortening of the silent period applies predominantly for TMS contralateral to the affected limbs (Cantello et al., 1991). Similar shortening of the silent period after TMS is seen in neuroleptic-induced parkinsonism (Priori et al., 1994). Treatment of Parkinson's disease patients with L-DOPA or biperiden lengthens the silent period toward normal values (Priori et al., 1994; Ridding et al., 1995a). Another way in which TMS can be used to demonstrate inhibition at the cortical level is with paired pulses, the EMG response to the second pulse being used

to measure duration of postexcitation inhibition produced by the first. Two studies (Ridding et al., 1995a; Berardelli et al., 1996) have shown that the magnitude of inhibition, so assessed, is less than normal in Parkinson's disease, and can be restored toward normal with L-DOPA therapy. This evidence of reduced inhibition in the cortex is what would be expected if the processes, which normally ensure selective activation of assemblies, were impaired, so that assemblies more readily "coalesce" in their activity, rather than exhibiting mutual inhibition.

Using ERP methodology, there is evidence that potentials signifying the early excitatory responses (P1 and P2 to a visual stimulus) are larger-than-normal in Parkinson's disease (Wright et al., 1993; see also Praamstra and Plat, 2001). Later potentials (such as the P300), which are indicative of inhibitory processes, are smaller than normal, especially when produced under conditions of high working-memory load, normally requiring stronger inhibition (Robertson and Empson, 1999). Pulvermüller et al. (1996) reported that P300 potentials were attenuated in Parkinson's disease, most severely when they were produced by a stimulus indicating a "NoGo" response, again normally involving especially strong inhibition.

An important aspect of the above data is that in several studies (Sharpe, 1992; Channon et al., 1993; Dalrymple-Alford et al., 1994; Katsarou et al., 1998), correlations between the cognitive deficit and the clinical scores of classic symptoms of Parkinson's disease are weak or nonexistent. This suggests that the classic symptoms arise in a different way from the cognitive deficits. One possible difference is that the classical symptoms of Parkinson's disease (akinesia, rigidity, and tremor) arise from pathology in the "motor" circuit of the basal ganglia (involving, *inter alia*, dopamine loss in the dorsal putamen), and, in the case of akinesia and rigidity, are expressed mainly via subcortical pathways rather than thalamo-cortical ones. In contrast, the impairments described above are likely the result of dopamine loss elsewhere (such as the caudate nucleus), and are expressed via thalamo-cortical links. One empirical study supports this (Holthoff-Detto et al., 1997). Using a PET method to assess the degree of loss of dopaminergic innervation, it was shown that, as the disorder progresses, dopamine loss from the caudate nucleus correlated with impairment in a cognitive task (delayed recall), but not with locomotor impairment (which correlated better with dopamine loss in the putamen).

It is however, noteworthy that, when posture or gait is monitored during performance of a cognitive or a motor task, the deficit in the tasks in Parkinson's disease correlates well with measures of postural instability, or increased variability of gait timing but not with global measures of motor impairment (Marchese et al., 2003; Yogev et al., 2005). This suggests that control of posture and gait uses processing resources in common with the concurrent tasks, while the processes involved for the classic motor symptoms do not. This is discussed further in the next section.

In addition to these specific predictions, a number of studies show that parkinsonian patients have difficulty in rapid deployment of (or shift between) foci of attention (implicitly involving shift of activity between cell assemblies). Flowers and Robertson (1985) showed that parkinsonian patients had difficulty in changing rules in an "odd-man-out" discrimination task, where the discrimination could be made on more than one dimension. Robertson and Flowers (1990) used a five-choice button-pressing task to assess learning and generation of sequences. Parkinsonian

patients could both learn and generate sequences, but were impaired in maintaining a sequence if two different ones had to be learnt, with requirement for switching spontaneously between sequences within a trial. Most errors consisted of reverting to the alternative pattern. Two studies show impairment in reversal of a previously acquired discrimination (Lichter et al., 1988; Swainson et al., 2000). Two other studies show that the most severe deficits occur not so much in reversal of the significance of stimuli *per se*, but in shift of the relevant dimensions (Downes et al., 1989; Owen et al., 1992). This is also tested in the "trails making tests" (version B), in which subjects have to join symbols on a page alternating between letters (to be joined in alphabetical order) and numbers (to be joined in numerical order). Parkinsonian patients were impaired in this task (Tamura et al., 2003). Hayes et al. (1998) used two set-shifting tasks. In the first, in training, subjects learnt to associate two colors with two responses and also two shapes with the same two responses. In experimental trials, the stimulus could be uni- or bidimensional (i.e., in the former case, either shapes or colors were relevant but not simultaneously, in the latter case both color and shape cues were present and relevant at same time). The word "color" or "shape" appeared simultaneously with the stimuli. Stimuli occurred in pairs. On one half of trials the instruction word for the second stimulus was the same as on the first member of the pair, while on the other it was different (therefore requiring switch of attention). RT was generally about 300 ms longer in parkinsonian patients than in normal subjects. The difference in RT between attention switch and no-switch (for the second members of each pair) was about 90 ms for normal subjects and about 184 ms for Parkinson's disease patients (and longer for hypokinetic or unimpaired patients on medication, than for patients with dyskinesias due to medication). In the second task, the letter A indicated tapping three points in an equilateral triangle in sequence 1,2,3, and the letter B indicated that the required sequence was 1,3,2. Letter pairs were then presented (any of AA, AB, BA, and BB) indicating a sequence of six taps, with shift of set required for AB and BA after the third tap, and no set shift required for AA and BB. RT difference between the third and the fourth tap was small for normal subjects (~100 ms) and did not differ for shift and nonshift conditions. In hypokinetic parkinsonian patients on medication the difference was ~270 ms for nonshift and ~550 ms for shift conditions. For unimpaired patients on medication the values were ~60 and 150 ms, and for hyperkinetic patients they were ~130 and 170 ms. Withholding medication increased the time to shift. Praamstra and Plat (2001) made use of the "Simon effect": In this paradigm, the letters A and B indicate responses with left and right hands respectively. If A and B themselves appear respectively to left and right of center (compatible condition), RT is faster than if they appear in the opposite (incompatible) positions (which requires inhibition of an automatic tendency). In their own experiment the authors showed that in Parkinson's disease the inhibition of the automatic tendency in the incompatible condition is weaker than in normal subjects. This was shown by the proportion of errors (high in parkinsonian patients). When there was a shift between trials from incompatible to compatible, normal subjects adjusted their responses on a trial-by-trial basis, but parkinsonian patients were more influenced by the immediately preceding trial. Thus the Simon effect (difference between compatible and incompatible) following an incompatible trial was 23 ms in the patient group but only 2 ms in normal subjects. A similar inflexibility in shifting from habitual response pattern was shown

by Dujardin et al. (1999) using the Stroop paradigm. Meiran et al. (2004) used a design where the correct response depended on which of two dimensions (up/down or left/right) was in operation. The dimension could be changed randomly from trial to trial, and was indicated by cues. Despite the cueing, parkinsonian patients performed at chance levels for responses dependent on identifying the shift of dimension, but were unimpaired when the dimension stayed constant, or when correct responding did not depend on recognizing the dimension in operation. In another demonstration of the impairment in parkinsonian patients, in shifting dimension (Shook et al., 2005), impairment was closely related to the unmedicated state.

The interpretation of these results is complicated. There are several rival hypotheses: Parkinson's disease patients may have a difficulty in relinquishing a previously relevant dimension (and so, in some situations, perseverate). Alternatively, they may have difficulty in "reawakening" a dimension, which had previously been suppressed (because the irrelevance of that dimension has been learned more strongly than normal). Finally, they may have difficulty in shifting dimensions, irrespective of the former two detailed strategies. Two studies investigate this. Owen et al. (1993) found that medicated parkinsonian patients have difficulty in realizing that a previously irrelevant dimension is now relevant, but not in realizing that a previously relevant dimension is now irrelevant. However, Gauntlett-Gilbert et al. (1999) found that difficulty in shift of dimension was present but was unrelated to the detailed mechanism (perseveration versus excess learning of the irrelevance of one dimension). These results are compatible with the theory of the basal ganglia advocated here, and its extension to parkinsonian syndromes, but do not permit specific explanations. As part of the pathophysiology of parkinsonism, there is widespread tonic overactivity in medium spiny neurons, including those of origin of both direct and indirect pathways. Therefore, in parkinsonism, task-related reduction of firing in such neurons (of either pathway) is likely to be more difficult than task-related increase in firing. This being so, impairment in task-related decrease in firing of the neurons of the indirect pathway would produce impairment in awakening previously suppressed cell assemblies, a mechanism identifiable as "excess learning of irrelevance." However, impairment in decrease in firing of neurons of the direct pathway would produce impairment in switching off previously active assemblies, identifiable as perseveration. From theory, a combination in either or both of these processes is expected to give rise to the difficulty in dimensional shift.

It should also be pointed out that the data reviewed in this subsection refer to attentional rather than micro- or macrobehavioral selection. It is therefore predicted that the impairments revealed should correlate with dopamine depletion in the caudate rather than the "motor" regions of the striatum (putamen). On this there is however currently no evidence.

8.4 INFLEXIBILITY OF ADJUSTMENTS OF POSTURE AND GAIT IN PARKINSON'S DISEASE

The previous section was concerned with selection of dimensions for attention and of behavior-related cell assemblies. Behavioral output should include automatic adjustments of gait or posture, normally thought of as "motor functions." In Parkinson's

disease there are, besides the classic motor symptoms, many abnormalities in gait and posture. Often these normal functions and their abnormalities in Parkinson's disease are spoken of in terms of "postural reflexes." However, there are several indications that these adjustments are not reflexes as commonly understood, but are generated by mechanisms similar to those underlying the cognitive processes just described.

Postural "reflexes" (so-called) can sometimes be examined experimentally in a controlled way. One example of this involves subjects standing on a platform, which, unpredictably, is given a sudden tilt, while muscle activity is recorded with EMG. For "toe-up" tilts, the muscle response includes a burst of activity in the ankle extensor muscles. The latency of such a response is longer than for any of the classic reflexes, and is adaptive with respect to global posture of the body, rather than in relation just to the particular joint or limb (as is the case for classic reflexes). Other indications that this response is not a true reflex are the following: The long-latency response is seen when the perturbation occurs with the body unsupported, but when the subject holds on to a frame, there is marked rearrangement of the response (Nardone et al., 1990). Thus the response seems to be guided by overall postural imbalance rather than by specific reflex actions. According to Beckley et al. (1991a, 1993), when the size of the perturbation is predictable, the size of the EMG response is adjusted to match. When one of two sizes of perturbation occurs randomly, the response size is chosen as a default to fit the larger of the expected perturbations, which is a safer way of ensuring overall balance. Bloem et al. (1995a) showed that "toe-up" perturbations in normal subjects could be switched on or off by instructions to "resist" or "yield" modifications not expected of reflexes. Another example of a postural "reflex" studied experimentally is the response to a small pull to the arm, in standing subjects, when there is a compensatory contraction of calf muscles. Traub et al. (1980) showed that this response occurred before stretch of these muscles, and was therefore something other than a classic reflex. Overall, such postural or gait "reflexes" can be adjusted adaptively by postural or cognitive "set," in a manner not expected of true reflexes. Likewise, it has recently become clear that posture is influenced by attentional processes in a manner similar to that found for cognitive tasks (see review of Woollacott and Shumway-Cook, 2002).

In Parkinson's disease, these automatic adjustments are impaired. For unpredictable "toe-up" tilts, parkinsonian subjects cannot adjust the size of the response to the expected size of the tilt nor can they chose the larger (safer) response size as a default when the size of the perturbation is uncertain (Bloem et al., 1995b). Similar impairments in selecting a default are seen in subjects administered neuroleptic drugs (Beckley et al., 1991b). In addition, parkinsonian subjects do not modify the postural adjustments in response to instructions to "resist" or to "yield" (Bloem et al., 1995a). Traub et al. (1980) found that the anticipatory calf muscle contraction, following an "arm tug" in standing subjects was absent or attenuated in many cases of Parkinson's disease, but was present in all of 50 normal controls. Defebvre et al. (2002) used a task where the subject raises one leg laterally. In normal subjects this leads to a long-latency "reflex" adjustment involving transfer of weight in the supporting foot toward the side of support. In this task, the speed of weight transfer was slowed in Parkinson's disease and restored to normal speed by L-DOPA.

Schettino et al. (2004) studied the details of hand-shape movements when a subject reaches for and grasps an object. Hand preshaping to fit the shape of a to-be-grasped object is impaired in Parkinson's disease, although the direction of the reach is not. That impairment in adjustment of posture in Parkinson's disease is determined by cognitive processes rather than true reflexes is shown by the fact (mentioned in the previous section) that impairment in concurrent cognitive tasks correlates with postural instability.

Not all of these impairments in gait and posture are remedied by L-DOPA (Blin et al., 1991), and not all of them are produced in normal subjects by administering neuroleptic drugs (Dietz et al., 1988; Beckley et al., 1991b). It has been suggested that this implies that they are produced in part by mechanisms other than absence of dopamine. However, strictly these results show that some of the impairments are independent of the *acute* effects of dopamine. They may yet be determined by *chronic* dopamine deficiency (not mimicked by single doses of neuroleptics nor remedied by acute administration of L-DOPA). In this context, it should be noted that striatal dopamine is a factor in instrumental learning, which includes learning at the motor level, mediated by "knowledge of outcomes." Many of the postural adjustments described in the previous paragraphs are probably laid down initially by processes akin to instrumental conditioning, as it applies to "microbehavior." During infancy, such motor learning is likely to be involved in initial acquisition of postural adjustments. During childhood and adolescence, when the size and weight of body segments is changing month by month, such motor learning is likely to be crucial for "fine tuning" of the same postural adjustments. In adulthood, size and weight of body segments change less, but the same motor learning processes are still likely to be in operation, to be used if necessary.

Since such motor learning involves dopamine as a cofactor, one would expect it to be impaired in Parkinson's disease. Evidence for this has been provided by Marsden (1982, figure 2) and Frith et al. (1986) in acquisition of tracking tasks, by Swinnen et al. (2000) in acquisition of interlimb coordination, and by Verschueren et al. (1997) in acquisition of more complex bimanual tasks. Learning by outcome is shown in an older task, the pursuit rotor tasks, where learning is slower than normal in Parkinson's disease (Harrington et al., 1990; Sarazin et al., 2002; but see Heindel et al., 1989). There is also some evidence that adjustment of visuo-manual coordination after vision distorted with prismatic lenses is impaired in Parkinson's disease (Canavan et al., 1990). However, this result was not replicated by Fernandez-Ruiz et al. (2003) and needs to be reexamined. These results are part of a larger body of evidence showing that the form of learning referred to as "procedural learning," is impaired in Parkinson's disease. However, this has been documented in tasks involving learning of complex sequences of behavior (Saint-Cyr et al., 1988; Pascual-Leone et al., 1993; Jackson et al., 1995; Vakil and Herishann-Naaman, 1998; Sommer et al., 1999; Helmuth et al., 2000). Impairment is thus not easily attributed to the single factor of loss of dopamine as a cofactor for learning, although this is likely to play a part.

The impairments in postural adjustments in Parkinson's disease, described above, probably reflect mainly an inability to select one program (cortical assembly) to the exclusion of others. However, each of these programs is likely to have been

acquired by a previous history of instrumental conditioning ("motor learning"). Motor learning situations in experimental tasks, and in children and adolescents who are still growing are far more novel than those to which most parkinsonian patients are exposed day-by-day. Thus, although there is impairment in motor learning, it may not be of overwhelming importance in Parkinson's disease. Nevertheless, some of the impairments of posture and gait, especially those not remedied by acute L-DOPA, may reflect a long history of impaired "fine tuning" of postural adjustments, normally mediated by instrumental motor learning, as well as failure to select (or inappropriate coactivation of) programs for posture and gait.

8.5 THE ROLE OF THE SUBTHALAMUS IN PRODUCTION OF PARKINSONIAN SYMPTOMS

In Section 3.4.2, evidence was reviewed that in parkinsonian syndromes, firing rate in STN neurons is markedly elevated, this being due mainly to loss of a direct dopaminergic inhibitory effect, rather than an indirect effect of striatal dopamine denervation. The importance of STN in production of parkinsonian symptoms is reinforced by the paper of Bergman et al. (1990), who showed in MPTP-treated monkeys, that an ibotenic acid lesion of STN reduced all major motor abnormalities in contralateral limbs (akinesia, tremor, and rigidity). Purposeful movements were regained and tremor was almost completely absent. The result was replicated in primates by Aziz et al. (1991). Subsequently, Wichmann et al. (1994b) found, in MPTP parkinsonian monkeys, that muscimol injections into STN, which blocked all activity there, also reduced akinesia, tremor, and rigidity, as well as producing contralateral dyskinesia. (Bicuculline injections into STN, which blocked the inhibitory input from GPe, increased firing rate there only slightly, therefore suggesting that there was only a low degree of tonic inhibition from GPe. In contrast to inactivation of STN, this procedure did not change parkinsonian symptoms.) There is parallel evidence in rats of STN lesions reducing symptoms of basal ganglionic disorder: Henderson et al. (1999) found that STN lesions reduced, but did not abolish rotational asymmetries in dopamine-denervated rats given apomorphine. The same result was reported by Jeon et al. (2003). It is noteworthy that, in the paper of Bergman et al. (1990) in monkeys, STN lesions left some remaining impairment (akinesia and clumsiness) due to dopamine depletion: Similarly, Henderson et al. (1999) found that STN lesions had no beneficial effect on either sensory neglect or skilled paw reaching. Jeon et al. (2003) found some improvement in the deficit in "forepaw adjustment" movements, but the effect of STN lesions was much smaller than that on rotatory behavior. Nevertheless, in view of the evidence of direct effects of dopamine in the subthalamus and the effect of STN lesions in reducing many symptoms of basal ganglionic disorder, the excessive firing of neurons in STN has to be regarded as a major factor in producing the classic symptoms of Parkinson's disease. It is incorporated into the analysis below of parkinsonian tremor (Section 8.6). Following this, the direct influence of STN on brain-stem nuclei, notably the pedunculopontine nucleus (PPN) is explored (Section 8.7.1), leading to further analysis of the symptoms of akinesia (Section 8.7.2) and rigidity (Section 8.7.3).

8.6 BURST FIRING IN COMPONENTS OF THE BASAL GANGLIA AND PARKINSONIAN TREMOR

As mentioned above, tremor is one of the symptoms alleviated by STN lesions in parkinsonian monkeys (Bergman et al., 1990). Parkinsonian tremor in humans is also alleviated by pallidal lesions (Dogali et al., 1995) and by lesions of the motor thalamus (Tasker et al., 1983, 1997; Burchiel, 1995; Moriyama et al., 1999). Thus the explanation of parkinsonian tremor is likely to involve pathways through the motor thalamus, rather than through direct descending pathways to the brain stem. This conclusion is supported by the fact that lesions of the PPN, although producing akinesia (see Section 8.7.2), fail to reproduce the tremor of Parkinson's disease (Kojima et al., 1997).

It is however clear that parkinsonian tremor cannot be adequately understood just in terms of the relative over- or underactivity of neurons in the various subdivisions of the basal ganglia, although that is certainly an important factor. One of the possible implications is that the pattern of firing, as well as the frequency of firing is an important determinant of this symptom. Parkinsonian tremor also implies that some sort of oscillatory neural activity appears as a result of dopamine depletion in the basal ganglia. In the following section, the idea is explored that abnormal burst firing is present in parkinsonism, and sometimes, when it becomes rhythmic, this can give rise to parkinsonian tremor.

Direct evidence for burst firing in parkinsonian syndromes comes from several papers. Filion (1979), using macaque monkeys, compared firing patterns in GPe and GPi before and after an electrolytic lesion of the SNC. In normal animals GPi neurons fired in an irregular nonbursty, nonrhythmic fashion. After the lesions, 40/169 GPi units fired spikes grouped in a continuous succession of bursts, which persisted through movement, and during both waking and sleep. There were up to 30 spikes in each burst, at rates of up to 600–800/s, with intervening silent periods of 10–100 ms. Across the series of animals, the proportion of GPi neurons showing such bursting was related to the proportion of SNC destroyed by the lesion. In GPe in normal animals, firing patterns were similar to those of neurons in the normal GPi, but there were interposed periods of silence lasting up to several hundred milliseconds. After the lesion the long periods of silence were almost absent and a large number of cells displayed burst firing, though not in such a continuous succession as in GPi. Bursting was generally more prominent on the side of a unilateral lesion. It was also found that the D2-blocker haloperidol in doses producing parkinsonian symptoms produced bursting in 19 (61%) of 31 cells in GPi. Filion and Tremblay (1991) confirmed, in MPTP-treated cynomolgus monkeys, that neurons in both GPe and GPi displayed abnormal bursting, not seen in intact animals. Interspike interval (ISI) histograms in intact animals had a modal interval of 8 ms in GPi and 7 ms in GPe. In MPTP-treated animals these values fell to 4 ms in both structures—indicative of fast intraburst timing. In GPe but not GPi there was also an increase compared to normal in the number of intervals greater than 100 ms (1.1% in normals, 4.8% in treated animals). Bergman et al. (1994) found, in African green monkeys, that in the normal state in STN and GPi, 69 and 78% of cells, respectively, had burst discharges, while these values increased to 79 and 89%, respectively, after MPTP (and average burst duration fell from 121 to 88 ms in STN and from 213 to 146 ms in GPi).

Ni et al. (2000) reported that, in normal urethane-anesthetized rats, GP neurons fired at a rate of 22.1 ± 1.4 Hz, firing being regular in 45% of cells, irregular in 49%, and bursty in 6%. After 6-HD lesions of SNC, no change in firing rate occurred but the proportion of cells with bursty properties had increased to 27%, with no change in the proportion of irregularly firing units. Bursting was indicated by a modal ISI of around 20–30 ms (sometimes with periods of complete silence for several seconds in between bursts). The ISI histograms became more skewed as a result of the lesions. Other demonstrations, in rat parkinsonian models, of the increase in burst firing have been provided for pallidum (=GPe) by Pan and Walters (1988; but see Chang et al., 2003) and for SNR by Burbaud et al. (1995), Tseng et al. (2001b), and Chang et al. (2003). Burst firing in STN in parkinsonian animals has also been described (Bergman et al., 1994), although details of burst structure are not provided. *Significantly, several studies have found that burst firing in GP or SNR can be normalized after subthalamic lesions.* This was found in rats for pallidum (=GPe) by Ni et al. (2000) and for SNR by Burbaud et al. (1995), Murer et al. (1997), Tseng et al. (2001b), and Chang et al. (2003).

A possible mechanism leading to increase of burst firing in parkinsonian animals is suggested by a number of studies by Nakanishi and colleagues, of firing patterns in slice preparations of component structures of the basal ganglia. These papers have reported, for rat slices, that regular tonic activity occurs in the major neuron types in each of pallidum (=GPe; Nakanishi et al., 1985), EP (=GPi; Nakanishi et al., 1990), STN (Nakanishi et al., 1987a), and SNR (Nakanishi et al., 1987b). Generally such tonic activity has frequencies ranging between 1 and 40 Hz. Depolarizing pulses can increase the frequency of tonic firing in these structures, which shows little spike frequency adaptation and can reach frequencies as high as 300–500 Hz for large current injections. This stable tonic discharge presumably implies that the resting membrane potential of cells in these structures is relatively depolarized, and values of −40 to −65 mV are specifically given for the membrane potentials of neurons in STN (Nakanishi et al., 1987a). Most significantly, Nakanishi and colleagues report for EP (Nakanishi et al., 1990), STN (Nakanishi et al., 1987a), and SNR (Nakanishi et al., 1987b) that when neurons are held at potentials more negative than −65 mV, sudden cessation of the hyperpolarizing current pulse or introduction of a depolarizing pulse leads to brief high-frequency burst discharge, superimposed on a slow calcium spike of 50–100 ms duration, not seen under control conditions at the same membrane potential (see Figure 8.2). Burst firing in similar circumstances has also been reported by Nambu and Llinas (1990) in slices of guinea pig globus pallidus (=GPe).

Burst firing, superimposed on slow calcium spikes occurs in neurons in a variety of brain structures (Huguenard, 1996). Typically the calcium spikes emerge when membrane potential is raised from hyperpolarized level to a threshold level at around −55 mV (a threshold more negative than that for typical action potentials). The calcium spike lasts up to 50–100 ms. With extracellular recording, the bursts have a characteristic internal structure, with the first ISIs being short (6 ms or less) and later ISIs in each burst becoming longer (e.g., Gerber et al., 1989). In *in vivo* experiments on parkinsonian animals, intracellular recording and biophysical analysis is not possible. None of the extracellular studies in such animals of neuronal

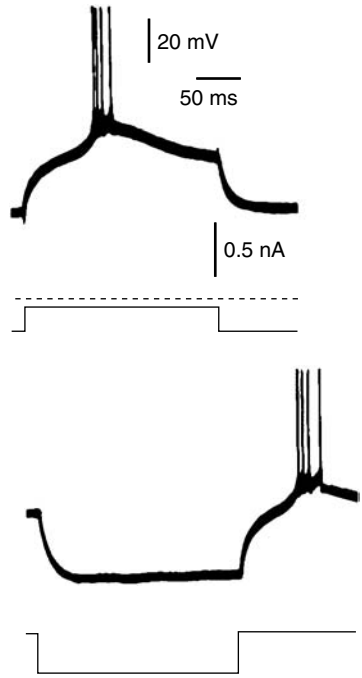

FIGURE 8.2 Burst firing in rat SNR neurons on relief from sustained hyperpolarization studied *in vitro*. (Reprinted from Nakanishi, H., Kita, H., and Kitai, S.T. *Brain Res.*, 437, 45–55, 1987. Copyright [1987], with permission from Elsevier.)

"bursting" in pallidum or EP analyze within-burst internal structure in a systematic way (although in figure 1C of Ni et al. [2000], ISI sequences are similar to those in bursts arising from calcium spikes). More work is required to prove that burst firing in nuclei of the basal ganglia in parkinsonian animals reflects increased occurrence of low-threshold calcium spikes.

Despite this area of uncertainty, with the above results in mind, it is plausible to suggest that the bursting seen in parkinsonian animals in pallidum, EP, and SNR is the result of a combination of excessive inhibition and episodes of excessive excitation. Specifically, in these structures, excessive striatal activity, characteristic of parkinsonian states (see Section 3.4.5) provides a powerful tonic *inhibitory* drive and a prevailing degree of hyperpolarization not otherwise seen *in vivo*. Upon this can be superimposed periods of excessive *excitatory* drive from STN. Together they are equivalent to the conditions seen *in vitro* (Figure 8.2) leading to burst firing. The fact that STN lesions can reduce burst firing in parkinsonian animals in neurons of GP and SNR fits this proposal. Moreover, it has been reported (Filion et al., 1991) that apomorphine given to parkinsonian monkeys can regularize the firing in GPi, if given in doses that do not completely silence GPi neurons. These two observations represent loss of each of the interacting influences, which, it is proposed, lead to burst firing.

Several of the papers which document burst activity in parkinsonian syndromes also describe *rhythmic* bursting in structures of the basal ganglia, and there is

also a body of research relating rhythmic neural activity in the basal ganglia to parkinsonian tremor. In cynomolgus monkeys Filion (1979) found that burst firing in SNC-lesioned animals was sometimes rhythmic at a frequency around 15/s, markedly regular in some neurons, and at other times irregular. In the same species, according to Filion and Tremblay (1991) after MPTP treatment the abnormal bursting in GPe and GPi neurons could occur for short periods at 5–8 Hz, when it was accompanied by limb (mainly proximal) or axial tremor. The same neurons also bursted at higher frequency, again for short periods (often ~15 Hz) when no tremor was seen. Bergman et al. (1994), found in African green monkeys, that in the normal state, very few STN cells showed periodic oscillatory activity. After MPTP treatment 16.3% of STN cells showed strong rhythmic bursting close to the tremor frequency (average 6.0 Hz) with burst durations of 45 ± 23 ms appearing to increase just before the onset of tremor. Another 10% showed oscillatory activity at higher frequency (average 14.4 Hz). However, for the higher-frequency rhythmic bursting, oscillations were damped more strongly than for that at the tremor frequency (mean of only 4.8 peaks in autocorrelation histograms, compared to 8.6 in the autocorrelation histograms of the cells oscillating at 4–8 Hz). In GPi, the proportion of cells oscillating at 4–8 Hz increased from 5 to 25% after MPTP, plus about 12% with higher-frequency oscillations (mean 10.5 Hz). Similar results were obtained by Raz et al. (2000) in the same species. In the normal state 11% of GPe cells and only 3% of GPi cells showed significant 3–19 Hz oscillations. After MPTP treatment, a tremor appeared focusing around two frequencies: 5–6 and 11–12 Hz. Autocorrelation analysis of neuronal firing showed that 39% of GPe cells and 43% of GPi cells developed significant oscillations, with frequency bimodally distributed around 7 and 13 Hz. For 10% of these cells recorded during tremor periods, there was a significant tendency for tremor and neural oscillations to appear simultaneously. Nini et al. (1995) found in normal rhesus monkeys that very few (~1%) neuron pairs in GP (segment not stated) had CCHs suggestive of an oscillatory common input. After MPTP treatment a 7–11 Hz action/postural tremor appeared, and 19% of pairs had oscillatory CCHs (often giving 2 or 3 peaks on either side of origin). The frequency of oscillation or oscillatory correlation was bimodally distributed across neurons, with peaks at 5 and 10 Hz. Hutchinson et al. (1997a) report that GPi neurons recorded in human parkinsonian patients had accelerating/decelerating patterns of firing, at the same frequency as the tremor.

The coincidence of tremor frequency and neuronal burst frequencies in the two monkey species and the fact that rhythmic neuronal bursting sometimes occurred at the same time as tremor suggests that they are causally related. The question then arises as to the mechanism generating the oscillations and tremor. There are three possibilities: The rhythmic activity may be an intrinsic property of the neurons in GP of parkinsonian animals; it may be generated by network interactions within GP; or it may be an oscillation set up by circulation of influences around long loops involving the peripheral motor apparatus and sensory feedback. According to Nini et al. (1995), in MPTP-treated monkeys 35% of GP neurons became oscillatory but only 19% of pairs had oscillatory CCHs (often giving 2 or 3 peaks on either side of origin). This suggests that there is a rhythmicity intrinsic to the neurons, which only sometimes becomes coherent across neurons. Raz et al. (2000) found that, in normal

vervet monkeys, CCHs revealed no correlation between neuron pairs in 96% of cells in normal animals and oscillatory CCHs in only 1%. After MPTP 40% of CCHs had significant oscillations centered around 13–15 Hz. They comment that the fact that both low- and high-frequency oscillations were revealed by autocorrelation but only the higher frequency by CCHs suggests that the low-frequency rhythms are innate to neurons, while the high frequency ones are network effects.

Clearly there are both unsynchronized and synchronized oscillations in GP of MPTP animals. Unsynchronized oscillations are likely to represent one of the manifestations of the burst discharge condition discussed above. However, it is not clear what the method of synchronization is: It may be due to activity relayed in local collaterals within STN, SNR, GPi, or GPe. However, only a few reports are available showing that such collaterals exist. François et al. (1984) showed that they do exist, but are not present for every cell, have few secondary branches, and no dense terminal arborizations. Kita (1993) reported for GP of rat that the main axon of a majority of efferent neurons emitted multiple collaterals within GP, which traveled within GP a long distance, and bore large boutons. If local collaterals were the basis for synchronization of oscillatory activity between neurons, one would expect phase delays of at most a few milliseconds, small compared to the tremor period, and related to the distance between neurons in a pair. However, according to Nini et al. (1995) phase shifts in oscillating pairs (which were consistent over time for each pair) were very widely distributed, with no relation to distance between neurons. Raz et al. (2000) found that phase shifts between coherently oscillating neurons were also very widely distributed, especially for GPi pairs, although showing a tendency to cluster around zero for GPe pairs. These details suggest that mechanisms other than local collateral interactions are involved in coordinating the phase coherence. Thus the most likely mechanism for coordination of oscillations is that, from time to time, spontaneous synchronization of rhythmically bursting cells may occur due to peripheral feedback loops with loop delays corresponding to the tremor period.* When this happens it is not a unitary rhythm, with coherent phase relations between all oscillating entities. Ben-Pazi et al. (2001) showed in parkinsonian patients that although frequency of tremor in different limbs was generally very similar, coherence of tremor in different limbs was generally low.

A variety of evidence throws light on the nature of these long loops. In parkinsonian syndromes, STN is more-than-normally responsive to somatosensory stimuli. This was shown by Filion et al. (1988) who report that, after SNC lesions, in GPe and GPi, neurons could often be driven passively by manipulation of the trembling segment. They found that, in intact monkeys only 17% of pallidal neurons responded to natural stimuli, typically to passive movements about a single joint and in a single direction. In MPTP-treated monkeys, however, more neurons responded more vigorously and

* A prediction follows from this: The tremor frequency (reciprocal of the loop time) should be higher in smaller animals, because conduction time around the loop should be less. In general, parkinsonian tremor in monkeys has a faster frequency than in humans. In rats the situation is unclear. "Vacuous chewing," a rhythmic tremor of the jaw occurring acutely after neuroleptic administration, has been claimed as a rodent equivalent of parkinsonian tremor, and it has a low frequency similar to that in humans. However, it is uncertain whether this has the same mechanism as parkinsonian tremor in humans.

less selectively. The responses consisted of increased neural activation, rather than suppression of tonic firing. This suggests that the responses are transmitted from the cortex via STN, rather than via the striatum. This inference is supported by the finding of Wichmann et al. (1994b) that, in MPTP-treated vervets, the number of cells in GPi showing increases in firing rate with torque applications was reduced after additional STN lesions.

The main cause of parkinsonian tremor thus appears to be an indirect consequence of overactivity in STN. The fact that tremor in Parkinson's disease depends on pathological processes different from some other symptoms is shown in the study of Vingerhoets et al. (1997). Uptake of fluoro-DOPA in the striatum, assessed with PET, gave a measure of the degree of striatal dopamine loss. This correlated well with clinical scores of bradykinesia, but not significantly with tremor scores. Assuming tremor depends on the degree of subthalamic dopamine depletion, it would not have been measured by this PET method.

Zirh et al. (1998) investigated patterns of neuronal bursting in the thalamus in parkinsonian patients and tried to distinguish between two hypotheses to explain the parkinsonian tremor. If there was an intrinsic thalamic oscillator, it would be expected (from other knowledge about thalamic mechanisms) to reflect low-threshold calcium spikes, which produce bursts with initial short ISIs that become progressively longer. Alternatively if there was an unstable long-loop reflex arc, it would be expected to produce a quasi-sinusoidal accelerating/decelerating ISI pattern. Empirically, the pattern expected of an intrinsic thalamic oscillator was found in only 1/118 cells. An accelerating/decelerating pattern was seen more commonly, in about one-fifth of cells. Similar results were reported by Magnin et al. (2000): In extracellular thalamic recordings in human parkinsonian patients, the only burst firing seen to be locked to tremor (in 35% of cells in the ventral division of VLp) did not have the characteristics of those associated with low-threshold calcium spikes, typical of intrinsic thalamic oscillations. From other studies this neural oscillation lags tremor in thalamic nucleus ventralis caudalis but leads the tremor in other nuclei (Lenz et al., 1985, 1994). More specific evidence that sensory modulation is likely to contribute to the thalamic rhythm is that not only the pallidum-recipient, but also the cerebellum-recipient thalamic nuclei showed oscillatory firing correlated with tremor. Similar evidence was obtained by Hua et al. (1998). Analysis of spike trains during parkinsonian tremor revealed neither calcium spike-associated bursts nor a maximal tremor in pallidal-recipient thalamic nuclei. CCH, latency, and transfer function analysis indicated that sensory feedback is a critical element in the relationship between thalamic activity and parkinsonian tremor. Such evidence suggests that parkinsonian tremor is mediated by either unstable long-loop reflexes or sensory modulation of a central oscillator. Both mechanisms involve the influence of ascending sensory signals. Presumably the great benefit for parkinsonian tremor of VL thalamotomy is due to the lesions breaking the long loops, in which resonant activity occurs to produce tremor, a mechanism very different from that by which STN lesions are proposed to alleviate akinesia. Older evidence has shown that peripheral deafferentation does *not* abolish tremor in parkinsonian monkeys (Lamarre and Joffroy, 1979) and in parkinsonian patients (Foerster, 1911; Pollak and Davis, 1930). However this finding does not refute the proposed mechanism, because deafferentation could change "amplitude, rhythm, and rate."

8.7 DIRECT CONNECTIONS FROM BASAL GANGLIA TO BRAIN STEM, AND THEIR ROLE IN PARKINSONIAN AKINESIA AND RIGIDITY

Two symptoms given prominence in descriptions of Parkinson's disease—akinesia and rigidity—are improved little by thalamotomy, unlike the symptom of tremor (see Section 8.6), although all three symptom classes are alleviated by STN lesions. Akinesia and rigidity are often associated in Parkinson's disease, and appear to represent a subtype different from that in which tremor predominates (see Section 8.1). Jellinger (1999) suggests, on the basis of neuropathological studies, that in this subtype, dopamine cell loss is predominantly in the lateral part of substantia nigra, which innervates the motor part of the striatum (dorsal putamen). It is difficult to incorporate this finding in detail into the scheme of functional circuits through the basal ganglia (mentioned in Section 2.2), without fuller data on dopamine loss in parts of the basal ganglia (such as STN) additional to the striatum. Nevertheless, the fact that akinesia and rigidity change little with thalamotomy suggests that direct pathways from the basal ganglia to the brain stem, not involving thalamo-cortical links, might be involved in these two symptoms. Before they can be analyzed, it is necessary to introduce more basic information about such descending pathways in the normal brain.

8.7.1 Projections from GP and STN to the Pedunculopontine Nucleus

The output nuclei of the basal ganglia (SNR and GPi) send projections not only to the thalamus but also to brain stem structures such as the superior colliculus (Harting et al., 1988; Williams and Faull, 1988; Deniau and Chevalier, 1992; Redgrave et al., 1992; Takada et al., 1994) and the pedunculopontine nucleus (PPN) (Nauta and Mehler, 1966; Filion and Harnois, 1978; Larsen and McBride, 1979; Harnois and Filion, 1980, 1982; Noda and Oka, 1984; Kang and Kitai, 1990; Spann and Grofova, 1991; Shink et al., 1997). The pathways from GPi and SNR to PPN are known to be inhibitory (Noda and Oka, 1986; Granata and Kitai, 1991). PPN also receives descending inputs from STN (Hammond et al., 1983; Jackson and Crossman, 1983; Kita and Kitai, 1987; Steininger et al., 1992), which, like other STN outputs are known to be excitatory (Granata and Kitai, 1989).

PPN itself consists of two parts (see review by Pahapill and Lozano, 2000), the *pars compacta*, more than 90% of whose neurons are cholinergic, and the *pars dissipatus*, with a much smaller proportion of cholinergic neurons, the remainder probably being mainly glutamatergic (Mesulam et al., 1989). Inhibitory inputs to PPN from SNR and GPi terminate mainly on its noncholinergic cells (Rye et al., 1995; Shink et al., 1997; Spann and Grofova, 1991; but see Kang and Kitai, 1990). The type of neuron on which the excitatory inputs from STN terminate is not known. However, as may be expected from the input pathways, some units in PPN show excitatory responses and some show inhibitory responses related to a trained movement in roughly equal numbers (Matsumura et al., 1997). It is plausible to suggest that the former receive excitation from STN, while the latter receive inhibition from GPi/EP, but this was not revealed in their experiments.

Both segments of the nucleus give both ascending and descending connections. There is a major ascending cholinergic projection from PPN neurons to the thalamus, which is thought to project to all thalamic nuclei in rat, cat, and monkey. In rat it has been estimated that 60% of cholinergic PPN cells project to the thalamus and 90% of PPN inputs to the thalamus are cholinergic (Sofroniew et al., 1985). Generally, the cholinergic projection to the thalamus from the tegmentum has excitatory effects, as part of the classical reticular activating system.

Both PPN and superior colliculus can influence motor output by direct descending connections, avoiding relay through thalamus and cortex. Disruption or exaggeration of activity in these pathways as a result of disorders of the basal ganglia could change motor control functions in addition to any effect exerted via the motor thalamus. These effects could then appear to be ones exerted on the expression of coordinated motor function *sensu stricto*, rather than on behavioral or attentional selection. That subcortical outflow from the basal ganglia is important is shown by experiments, where the behavioral effects of microinjection of a GABA agonist into SNR is not abolished by removal of the telencephalon (Papadopoulos and Huston, 1980) or by hemitransection rostral to the substantia nigra (Reavill et al., 1981). According to Lee et al. (2000), the caudally-directed pathway from PPN, which includes both cholinergic and noncholinergic components, is involved in initiation, control, and termination of automatic motor performance such as gait (see also Pahapill and Lozano, 2000).

8.7.2 Akinesia and the Influence of the Basal Ganglia on the Pedunculopontine Nucleus

In Section 3.4.3.1, evidence was mentioned that the firing rate of GPi neurons was increased in parkinsonian syndromes. A possible explanation of parkinsonian akinesia is that there is increased inhibition of cells in the motor thalamus and therefore activity and excitability in cortical cell assemblies containing neurons in the motor thalamus is reduced. There is some evidence compatible with this, showing that psychophysiological correlates of movement are reduced in Parkinson's disease: Simpson and Khuraibet (1987) showed that the "readiness potential," a cortical potential occurring as motor acts are prepared, is reduced in duration and amplitude in parkinsonian patients, the degree of reduction fluctuating in proportion to short-term severity of symptoms. Likewise, Pulvermüller et al. (1996) reported that the "contingent negative variation," another preparatory potential, was reduced in amplitude in Parkinson's disease. Ellaway et al. (1995) showed that the motor cortical threshold for excitation by transcranial magnetic stimulation was elevated in Parkinson's disease, the degree of elevation correlating well with the severity of bradykinesia. Metabolic activation of the cortex during motor tasks is reduced in Parkinson's disease (Rascol et al., 1992; Playford et al., 1992). Pallidotomy, which relieves the symptoms of Parkinson's disease, increases the metabolic activation of cortical activity during motor tasks (Ceballos-Baumann et al., 1994; Grafton et al., 1995).

Despite the appeal of such evidence, it is unlikely that the increase in inhibition of the motor thalamus is the main cause of parkinsonian akinesia. Were this to be so, the increase in inhibitory output of GPi should result in silencing of the critical

pallidal-receiving neurons in the motor thalamus, and so should be mimicked by lesions of the motor thalamus. However, experience with stereotactic thalamotomy shows that such lesions neither produce nor alleviate akinesia in Parkinson's disease (Marsden and Obeso, 1994; Burchiel, 1995), although akinesia is improved after both pallidotomy (Dogali et al., 1995; Lozano et al., 1995; Baron et al., 1996) or STN lesions (Bergman et al., 1990). Likewise, in hemiparkinsonian rats postural asymmetry was in no way diminished by lesion of the motor thalamus (Reavill et al., 1981). Moreover, one cannot resolve this paradox by invoking burst firing in the input from the pallidum to the thalamus: Akinesia presumably corresponds to silencing of some stage of the output from the basal ganglia, not burst firing within it (which is more likely to result in phasic symptoms). The paradox can be resolved only by considering outputs from the basal ganglia by routes other than the thalamus and cortex. As discussed above (Section 8.7.1) such outputs—to superior colliculus and PPN—are well documented, and their role in some parkinsonian deficits is indicated by the partial persistence in rats of these deficits after removal of telencephalic structures.

In Part I of this work, it was argued that cessation of inhibition in specific lines from GPi/SNR to the motor thalamus led to the release of specific behavioral programs. The role of descending influences from STN and GPi to PPN may be different. One possibility is that the detailed programming of behavior involves thalamo-cortical networks, while PPN is concerned with "switching" on or off a modulatory influence facilitating motor activity in a more general way. That the pathway via PPN acts as a switch rather than as a site for coding specific details of a behavioral program is suggested by the fact that the ultrastructure of PPN gives no indication of specific labeled lines, as does that of GPi or SNR (Moriizumi et al., 1989; Honda and Semba, 1995).

It was shown by Dunbar et al. (1992) that if excitotoxic lesions damaged the noncholinergic part of PPN, motor impairments in rats were produced, which were absent if the lesion affected only the cholinergic part. In experimental primates, Kojima et al. (1997; see also Matsumura and Kojima, 2001) showed that lesions of PPN can produce contralateral symptoms similar to hemiparkinsonism in the monkey. The actual symptoms described were flexed posture and hypokinesia in both upper and lower limbs. No tremor was observed. (Rigidity after such lesions is discussed below.) In experimental primates, akinesia after PPN lesions has also been reported by Aziz et al. (1998), Munro-Davies et al. (1999), and Nandi et al. (2002b). In a single human case, gait disturbance has been seen by Masdeu et al. (1994) after a circumscribed lesion including this nucleus. The role of PPN in human Parkinson's disease is also shown in a recent study finding that both gait disturbance and postural instability can be alleviated by low-frequency electrical stimulation of PPN (Plaha and Gill, 2005).

Kojima et al. (1997) ascribe the effects produced in their experiments to reduced excitatory input on midbrain dopamine neurons. However, in view of the fact that the syndrome only partially reproduces full parkinsonism, it is more likely to be an effect on a circumscribed output pathway of the basal ganglia. This suggests a hypothesis for true parkinsonian akinesia: The neurons in PPN with descending pathways which can control motor programs such as those for gait and other movements are silenced

by excessive activity in inhibitory projections from GPi. Direct support for this is that, in MPTP parkinsonian monkeys, the GABA antagonist bicuculline, injected into PPN reverses akinesia (Nandi et al., 2002b), although (in contrast to L-DOPA) it has no effect on tremor. Since the excessive inhibitory activity in projections to PPN from SNR and GPi is likely to result from excess activity in STN, this hypothesis is also compatible with the results of Bergman et al. (1990) and others, that STN lesions eliminate much of the akinesia of MPTP parkinsonism. In Section 4.7, it was suggested that the significance of the excitatory input from STN to GPi and SNR, is to ensure a high level of tonic activity in the latter nuclei, and thus to improve the temporal resolution of the superimposed pattern of pauses in this tonic activity resulting from inhibitory inputs. Following from this, the symptom of akinesia in Parkinson's disease arises because the STN excitatory input is so strong as to completely prevent inhibitory pauses making their appearance in the two output nuclei.

A prediction from this hypothesis is that, in akinetic parkinsonian syndromes, neurons in PPN with descending connections are silenced. This issue has not been well studied, and the limited evidence that has been produced is equivocal. In rat parkinsonian models, two studies (Breit et al., 2001; Jeon et al., 2003), find that PPN neurons, at least in anesthetized preparations, become *overactive*, this being reversed by STN lesions. In contrast, Ogura et al. (1997) report reductions of neuronal firing rates in PPN in parkinsonian rats. Since PPN has a diverse neuronal makeup, with some neuron types being inhibited, others being excited from the basal ganglia, the resolution of this discrepancy may depend on identifying the neuron types or their subnuclear regional location.

A somewhat different hypothesis is that, in human Parkinson's disease, neurons of PPN have degenerated. In several postmortem neuropathological studies this has been reported (Hirsch et al., 1987; Jellinger, 1988; Zweig et al., 1989; Gai et al., 1991). Whether this is a primary pathology in Parkinson's disease, complementary to the loss of dopamine neurons in SNC, or a secondary result appearing at an advanced stage of the disease is not clear at present. In this context, a syndrome called "pure akinesia" (without rigidity or tremor) should be mentioned. It may occur in patients whose urinary dopamine excretion is subnormal, and is then alleviated with L-DOPA treatment (Barbeau, 1972). This is presumably a variant of Parkinson's disease. Another type of pure akinesia is resistant to treatment with L-DOPA and is not accompanied by reduction of homovanillic acid (HVA) in cerebrospinal fluid (Imai, 1996). This may be a reflection of cell loss in PPN, with no (or lesser) involvement of dopaminergic cells in SNC. However, such cell loss is not necessary for akinesia to appear in human Parkinson's disease nor in animal parkinsonian models: It is established that PPN receives excessive descending inhibition from the basal ganglia in parkinsonian states, and the blocking of this inhibition alleviates akinesia (presumably because the neuronal population is intact and no longer inhibited). Moreover, akinesia can be produced in both animals and humans by administration of dopamine-blocking drugs, which do not lead to cell loss in PPN. Shima et al. (1996) reported that in most cases of Parkinson's disease (characterized by bradykinesia with akinesia), unit activity in GPi was greatly elevated and the symptom of akinesia was alleviated by postero-ventral pallidotomy. In 4 out of 82 cases however, increase in unit activity was far less prominent, and there was no lasting improvement in

akinesia after pallidotomy. In these cases, the primary cause of the akinesia may have been loss, rather than excessive inhibition of neurons in PPN.

Since the inhibitory projections from GPi are targeted mainly at the noncholinergic PPN neurons, either version of the hypothesis fits the results of Dunbar et al. (1992) where motor deficits were produced in rats by lesion of the noncholinergic part of PPN. However this does not fit in detail with the results of Aziz et al. (1998), where the lesion was stated to be "almost certainly" in the cholinergic part, nor those of Zweig et al. (1989) where cell loss (correlated with the degree of pre-mortem akinesia) was found in the lateral part of PPN pars compacta, where cholinergic cells normally predominate.

8.7.3 Parkinsonian Rigidity

Rigidity—an increase in muscle tone regardless of the usual reciprocal control of tone in agonist and antagonist muscle groups—is a symptom of Parkinson's disease clearly in the realm of motor coordination rather than behavioral selection. Like tremor, it involves activation of the motor apparatus. According to Bergman et al. (1990) rigidity is one of the symptoms which are alleviated by STN lesions in parkinsonian monkeys (see also Wichmann et al., 1994b). Conversely, irreversible blockade of dopamine receptors in STN (which increases impulse activity there) leads to an increase in muscle tone (Hemsley et al., 2002). These facts are compatible with either thalamo-cortical pathways or subcortical ones (via PPN) being implicated in production of rigidity. A major issue is thus whether the effect of STN lesions on rigidity is mediated via its influence on the motor thalamus or on PPN. The paragraphs below deal with the two possibilities in turn.

If the thalamus is involved in producing rigidity, one might expect a widespread excess of activity of the neurons in the motor thalamus to be associated with this symptom. This possibility appears to be in conflict with the finding of increased impulse activity in the inhibitory pathways to the motor thalamus from GPi and SNR. It is known that striatal neurons are overactive in parkinsonian syndromes. If, for some reason, that overactivity was distributed particularly in the neurons of origin of the direct pathway, inhibition of thalamic neurons from the basal ganglionic output nuclei could be reduced or absent. Rather than selected subsets of the inhibitory pathways to the motor thalamus being silenced (as is predicted to be the case in normal active behavior), this would need to be a uniform reduction of inhibitory tone across all or most afferent lines to the motor thalamus.

If the above reasoning holds, one would still expect neuronal firing rates to be increased when rigidity is present. There are very few reports of single-unit recording in the motor thalamus studied in relation to the symptom of rigidity. In one such study, where unit recording was made in the thalamus in MPTP-treated parkinsonian vervet monkeys, with rigidity and akinesia (Pessiglione et al., 2005), firing rates were the same as normal, although correlation between neurons was increased above normal, and specificity of impulse activation on passive manipulation of different joints was reduced.

Further doubt is cast on this model of rigidity by the results of Bergman et al. (1990) and Wichmann et al. (1994b). If the model were correct, lesion or inactivation

of STN should reduce the excitatory drive on neurons in GPi and SNR, which would then deliver less inhibition to the motor thalamus. Rather than alleviating rigidity (the observed result, albeit incomplete), one would expect, from the above model, that such lesions would exacerbate such a "positive" symptom.

The above reasoning would also lead one to expect that lesions of the motor thalamus would reduce the symptom of rigidity. Some studies report that VL thalamotomy can ameliorate the symptom of rigidity (Cooper et al., 1968; Moriyama et al., 1999). However, other reports suggest that this improvement is less complete than the improvement of tremor by such surgery, and the benefit tends to wear off over time (Tasker et al., 1983; Burchiel, 1995). Thus it is not certain that rigidity is driven simply by neuronal activity in this thalamic nucleus. However, small discrete regions of the thalamus may be related to rigidity: Narabayashi (1968) provides evidence to define such a region: Rigidity could be enhanced in parkinsonian patients by electrical stimulation, and was persistently alleviated by small lesions in the region so defined.

Similar paradoxical results have been obtained in animal experiments: Catalepsy is a syndrome produced in animals (for instance, by administration of neuroleptic drugs) with similarities to rigidity in humans (although affecting the whole of the motor apparatus rather than single limbs). If this syndrome involved relay of signals from the basal ganglia via the motor thalamus, one would expect neurons in the motor thalamus to be active (perhaps excessively so) when this syndrome is manifest. It is unknown whether such lesions in rats can alleviate pre-existing catalepsy, but lesions of nucleus VM (the major nucleus of the motor thalamus in this species) do not produce catalepsy (Starr and Summerhayes, 1983). However, contrary to the above model, injection of muscimol into nucleus VM, actually *produces* rather than alleviates catalepsy in rats (Starr and Summerhayes, 1983; Wolfarth et al., 1985). This was also shown by Klockgether et al. (1986), who produced the same effect with NMDA antagonists microinjected into this nucleus. These effects were reversed, respectively by a GABA antagonist and an NMDA agonist. Wolfarth et al. (1985) also showed that catalepsy produced by haloperidol administered systemically can be relieved by blocking inhibition in the thalamus by local injections of picrotoxin. Overall, evidence for the direct involvement of the neuronal overactivity in the thalamus in production of rigidity in humans or catalepsy in rats is weak.

If a subcortical pathway via PPN is involved in generating the symptom of rigidity, it is likely that impulse activity of neurons in this nucleus would be reduced by an excessive inhibitory control from GPi (as appears to be the case for the symptom of akinesia). One would then expect that lesions or impulse suppression in PPN should reproduce parkinsonian rigidity as well as akinesia. Kojima et al. (1997) stated that "rigidity seemed positive in both upper and lower limbs, but was hard to evaluate" (see also Matsumura and Kojima, 2001). Other studies using PPN lesions (Aziz et al., 1998; Munro-Davies et al., 1999) did not comment on this issue. Further pieces of evidence favor the idea that subcortical pathways are involved in rigidity. Electrical stimulation of PPN reduces muscle tone (Lai and Siegel, 1990; Takakusaki et al., 2003, 2004). Likewise catalepsy, produced by systemic injections of a neuroleptic, is greatly reduced if inhibitory effects in PPN are abolished by local injections of picrotoxin (Miwa et al., 1996). One would also expect that blockade of neural

activity in PPN would reproduce the symptom of rigidity in normal animals. On this point, the evidence is unclear: In the experiments of Takakusaki et al. (2003), microinjection of muscimol into PPN in cats did not increase muscle tone, but this was performed on a decerebrate preparation which was rigid already, and may have been incapable of further increase in tone. The reduction of tone produced by electrical stimulation of PPN was nevertheless greatly attenuated by injection of muscimol into this nucleus. Likewise in anesthetized, decerebrate cats, atonia (similar to that accompanying rapid eye-movement sleep) produced by stimulation of PPN was prevented by injection of muscimol into PPN (Takakusaki et al., 2004). However, in two studies involving injection of muscimol into PPN in intact monkeys (Matsumura and Kojima, 2001; Nandi et al., 2002a) no mention is made of rigidity, although other effects were produced.

A further body of evidence favors the idea that subcortical pathways via PPN are implicated in parkinsonian rigidity. This symptom depends on afferent input to the CNS, since it is reduced by dorsal rhizotomy or local anesthesia of muscle afferents (Foerster, 1921; Walshe, 1924; Thompson, 1998). This is explained by the finding that enhanced activity of long-latency components of the stretch reflex occurs in Parkinson's disease (Tatton and Lee, 1975; Mortimer and Webster, 1979; Rothwell et al., 1983; Berardelli et al., 1983; Cody et al., 1986; Delwaide et al., 1991; Bergui et al., 1992; Meara and Cody, 1992; Bloem et al., 1994). In most of these studies, the degree of rigidity was found to correlate with the enhancement of stretch reflexes, suggesting that the former is explained by the latter, although some studies did not find this asssociation (Bergui et al., 1992), or suggest that stretch reflex enhancement is not the only determinant of rigidity (Rothwell et al., 1983; Cody et al., 1986). The exact nature of the overactivity of reflexes is not fully resolved. Thompson (1998) notes that the Golgi tendon organs normally inhibit a class of spinal interneurons ("1b"), but in Parkinson's disease, this inhibition is reduced or even turned to facilitation in correlation with the degree of rigidity (Delwaide et al., 1991). It is implied that descending control over spinal 1b interneurons, via a reticulospinal pathway, changes as a result of the disease. Since a descending pathway (from PPN) targets the nucleus gigantocellularis (one of the origins of the reticulospinal pathway), a role for reduction of activity in this pathway in increasing muscle tone in some cases of Parkinson's disease provides a consistent explanation of rigidity. This hypothesis is supported by recent results of Pötter et al. (2004) who found, in patients with Parkinson's disease, that high-frequency stimulation of STN also attenuated spinal stretch reflexes mediated by the 1b interneurons. Since the STN stimulation was likely to reduce the tonic activity in this nucleus, as well as descending inhibition from GPi to PPN, this study suggests that in Parkinson's disease, descending pathways lead to exaggeration of long-latency stretch reflexes.*

Bloem et al. (1994) found enhancement of these long-latency stretch reflexes in patients with Parkinson's disease of typical late onset, but not in early-onset cases, nor in young patients with MPTP-induced Parkinsonism. The authors suggest that, in late-onset Parkinson's disease, there is cell loss additional to that in SNC, whereas

* In this study the reflex responsiveness after stimulation was associated with overall change of parkinsonian symptoms, but it is not stated whether it was correlated with the specific symptom of rigidity.

in the two early-onset conditions it is limited to SNC. The authors suggest that a non-dopaminergic pathology might be the cause of the enhanced reflexes, and the symptom of rigidity, when it occurs in typical late-onset Parkinson's disease. Specifically they mention the noradrenergic coeruleospinal pathway. Such additional pathology might also include cell loss in PPN. However, rigidity is substantially alleviated by L-DOPA treatment (Webster and Mortimer, 1977; Indo and Takahashi, 1986). The change in activation of 1b interneurons is also reversed by L-DOPA (Delwaide et al., 1991). Clinical scores for rigidity correlate significantly (if not strongly) with loss of striatal dopamine as documented by fluoro-DOPA uptake (Vingerhoets et al., 1997). Thus there is substantial evidence that rigidity is related to loss of dopamine. Where and how dopamine acts to produce the symptom is unknown. Since there are dopaminergic fibers descending from the brain stem and diencephalon to the spinal cord (Commissiong and Neff, 1979), which might be involved in Parkinson's disease, it is even possible that this symptom is the direct result of dopamine denervation in the spinal cord, although one report finds that this innervation is intact in Parkinson's disease (Scatton et al., 1986).

Despite some gaps in the evidence, and unresolved issues, this body of evidence gives greater credibility to the idea that the symptom of rigidity is mediated by a subcortical pathway involving PPN, than by the involvement of thalamo-cortical pathways. However, as mentioned above, manipulation of neuronal activity in the motor thalamus does influence catalepsy in rodents, a probable model of rigidity in human patients. Thus we do not yet have a full explanation of the symptom of rigidity.

8.8 PARKINSON'S DISEASE: SUMMARY

The symptoms of Parkinson's disease are many and varied and are not to be explained by a single pathophysiological mechanism. As far as striatal dopamine depletion is responsible, a variety of symptoms can be explained in terms of the widespread overactivity of striatal medium spiny neurons, the origin of both the direct and indirect pathways, and the consequent difficulty in selectively releasing or selectively suppressing specific pieces of behavior. These abnormal processes, acting in different parts of the striatum, can act on behavior at different levels. "Macrobehavior" and "microbehavior" reflected in symptoms presumably involve similar dynamic mechanisms, but in different parts of the striatum. Thus some of the symptoms of excessive release and excessive suppression are exerted at the level of bodily movements, others at the level of cognitive processes. In the case of the latter, it becomes more difficult than in the normal situation to activate separately different configurations of neurons, so that active cell assemblies apparently tend to fuse together rather than being kept separate. Symptoms related to "macrobehavior" are not easily confused with an abnormality of motor coordination, but those related to "microbehavior," manifest as abnormality of adjustments of posture and gait, can be.

Apart from the striatum, there is dopamine depletion in STN leading to overactivity of STN cells. This appears to be important in producing the classic symptom triad, akinesia, tremor, and rigidity. Akinesia arises, at least in part, from an excessively strong inhibitory influence of the basal ganglia on PPN. Tremor is related

to burst firing appearing as a result of combined excesses of both excitatory and inhibitory influences on GP neurons. Their firing may then become unstable and rhythmic, and with oscillations becoming entrained in phase-locked long loops with the peripheral motor apparatus leading to tremor. The mechanisms generating parkinsonian rigidity are less clearly resolved, but probably depend, like akinesia, on excessive inhibition of PPN by GPi.

There are some suggestions that the regions of greatest dopamine depletion differ between parkinsonian states dominated by tremor as opposed to those dominated by akinesia and rigidity. Thus Paulus and Jellinger (1991) found that cell loss in the lateral substantia nigra (which supplies the dorsal caudate with dopamine fibers) was more severe in the akinetic/rigid variety of Parkinson's disease than in the tremor-dominant subtype. In the medial part of substantia nigra (which supplies the caudate) the differential between the two subtypes was much smaller. Otsuka et al. (1996) used PET to assess striatal dopamine depletion, finding that the depletion in putamen and caudate correlated with severity of akinesia and rigidity, but not that of tremor. Such evidence is not yet sufficient to be used in developing detailed accounts of the dependence of symptoms on abnormality in different functional circuits through the basal ganglia. In particular, dopamine depletion in nuclei other than the striatum (especially the subthalamus) may play an important role in determining symptoms, but has never been measured in studies seeking correlations with symptoms.

9 Dopamine-Dependent Psychosis

9.1 INTRODUCTION

The term "psychosis" has a checkered history. It first appeared in the nineteenth century, implying a "mental" disorder, in contrast to the older term "neurosis," which implied organic disorder of the brain. Today, in the English-speaking world these two terms have almost completely reversed their respective original meanings. Psychosis is held to have a physical basis in the brain, whether or not that is known. The term, as commonly understood, means that patients suffer "a break with reality." In other words, psychosis is a state characterized by delusions and hallucinations. There are many sorts of psychosis, some with clear evidence of an organic lesion, some without such evidence, but presumably involving dynamic disturbance of brain activity. Psychosis is not generally classed as one of the disorders of the basal ganglia. Usually, it is considered as one of the manifestations of schizophrenia. It may even be regarded as synonymous with schizophrenia. This complex disorder involves disturbed activity in most structures of the forebrain, although there is no clear focal lesion. However, there are many abnormalities in schizophrenia—mainly enduring traits*—other than psychosis, which is a transient state. Psychosis also occurs in bipolar disorder, as mania, whose underlying basis is not well defined, but has some overlap with schizophrenia.

The key fact that allows some forms of psychosis to be considered as disorders of the basal ganglia is that they can be effectively treated with dopamine-blocking drugs. Dopamine is found in the striatum at far higher concentration than in any other brain region. This suggests that such psychoses are due to overactivity of dopamine in the striatum, a hypothesis for which there is now direct evidence (see Section 9.2). A further indication that the striatum is important in the genesis of psychosis is related to the balance between two transmitters: dopamine and acetylcholine. It is well established that these two have opposed roles in the striatum, in relation to neuronal and psychomotor function. The same appears to be true for the functional disorder in psychosis. Definition of this oppositional role in psychosis features prominently in the final section of this chapter. Thus, whatever the root cause of overactivity of striatal dopaminergic systems (which will not be discussed here), dopamine-mediated psychoses should fall within the scope of the theory of the basal ganglia presented in Part I.

* An exposition of the theory of schizophrenia, presenting an integrated explanation of both the nonpsychotic traits, and the tendency to psychotic destabilization, is provided in a forthcoming work by R. Miller, *A Neurodynamic Theory of Schizophrenia and Related Disorders* (in preparation).

9.2 DEVELOPMENT OF THE DOPAMINE HYPOTHESIS OF PSYCHOSIS

The evidence relating dopamine to psychosis is well known, although it has usually been seen as supporting the "dopamine hypothesis of schizophrenia," rather than, more correctly, of the dopamine hypothesis of psychosis. The central aspects of the evidence from which this hypothesis developed are as follows: Antipsychotic drugs are dopamine antagonists, acting at the D2 receptors. Psychomotor stimulant drugs, such as amphetamine or cocaine, which lead to increased release of dopamine from nerve terminals in active form can precipitate psychotic states in people who have no prior psychopathology if given in large doses or for long periods. Furthermore, repeated doses of stimulant drugs given to experimental animals lead to "sensitization." That is, the threshold dose for stimulant action falls, and the effect produced by a given suprathreshold dose increases. People who are vulnerable to, or recently recovered from psychoses, appear to be in a similar sensitized state, because they can be precipitated into full-blown psychoses with doses of stimulants far lower than those required to produce psychosis in previously healthy persons.

Such evidence led naturally to the search for actual overactivity of dopaminergic mechanisms in psychosis. This search has pursued two lines of inquiry: Either there might be too many dopamine receptors or there might be too much release of the transmitter dopamine itself. The first of these alternatives has prompted a great deal of work, but has not received consistent support. The second alternative was more difficult to investigate until positron emission tomography (PET) methodology was developed for measuring release of transmitter dopamine *in vivo*. In the early 1990s, such a method was devised by which it was possible to estimate, in specific brain structures, the rate of conversion of a radiolabeled version of L-DOPA into the corresponding version of dopamine. With this method, several studies showed that actively psychotic patients had higher-than-normal rates of dopamine synthesis in the striatum (Reith et al., 1994; Hietala et al., 1995; Lindström et al., 1999). Generally, this was seen in psychoses associated with schizophrenia, but temporal lobe epilepsy patients also showed elevated synthesis rates, if, as is sometimes the case, they also showed psychotic symptoms (Reith et al., 1994). Dopamine in the striatum is synthesized within dopaminergic nerve terminals sufficient to replenish stores depleted when the transmitter is released. Therefore, these studies imply that the rates of dopamine release are increased in relation to psychosis. Another method using PET was developed to measure dopamine release after amphetamine challenge. If dopamine-binding drugs are given, dopamine binding to receptors competes with drug binding. Dopamine release can then be estimated by the displacement of such an exogenous dopamine-binding ligand from its receptor. With this method, it has been found in several studies that striatal dopamine release by amphetamine is greater than normal in schizophrenic psychoses (Laruelle et al., 1996; Breier et al., 1997; Abi-Dargham et al., 1998). Recent studies with these two methods have provided the best evidence we currently have of dopamine overactivity in psychosis.

The methods used in these studies do not permit very accurate localization of the regions showing greatest increase in dopamine release. However, of the three studies of L-DOPA conversion, two (Reith et al., 1994; Lindström et al., 1999) show

greater elevation in psychotic patients in the caudate nucleus than in the putamen, while the third (Hietala et al., 1995) finds the reverse. From a theoretical viewpoint, it is important to resolve this discrepancy, since the symptoms of endogenous psychoses are almost entirely in the cognitive rather than the motor/behavioral domain, and abnormality in the caudate rather than putamen would be expected. Whether motor/behavioral symptoms are also a feature of endogenous psychoses is not easy to determine, because these psychoses are generally a by-product of more pervasive disorders (usually schizophrenia), which may have their own motor symptoms even when active psychosis is controlled by medication (Owens et al., 1982). However, in stimulant-induced psychotic states, where the drug presumably acts to increase dopamine release equally in all striatal regions, without these complications, motor symptoms, described as "choreiform" have been documented (Rylander, 1972).

There are several possible mechanisms by which excessive dopamine release could come about. Most likely, however, is that there is an excess of impulse traffic in the midbrain dopamine neurons themselves. Thus, it is well known that stimulant sensitization in animals (closely related to psychosis in humans) has a substantial conditioning component (Robinson and Becker, 1986; Robinson and Berridge, 1993). This suggests that there is an exaggeration, associated with conditioning, of relatively normal functions of impulse-associated transmitter release in the dopaminergic terminals. In stimulant-induced psychosis this is not the only mechanism leading to excessive dopamine release, since amphetamine exerts a direct effect at the level of intracellular transmitter dynamics (promotion of "reverse transport" of dopamine from nerve terminal stores to the extracellular space) (Parker and Cubeddu, 1986). Other stimulant drugs such as cocaine act directly by blocking dopamine reuptake (Ritz et al., 1987). However, in psychoses of endogenous origin these processes are unlikely to be at work, and an exaggeration of impulse-associated dopamine release is probably the main mechanism involved. Various pathways control impulse traffic in the midbrain dopamine neurons (see Section 2.1). These include inputs from motivational centers such as the amygdala and hypothalamus, which analyze motivational significance of sensory input, and use the outcome to control the dopaminergic system in instrumental learning in sensorimotor tasks. However, psychosis is not primarily a disorder at the sensorimotor level, although it does involve perceptual and motor abnormalities. It is most distinctively a disorder at the level of cognitive processes and behavior derived from them. Therefore, it is unlikely that overactivity in afferents to the dopamine neurons related to immediate sensory input is the predominant cause of the increase in dopamine release in psychosis. It is more likely that there is an abnormality of control related to intrinsic (internal) activity in other centers of the brain, notably control from the cerebral cortex. An important implication of this idea is developed in Section 9.6.

9.3 NEURAL DYNAMICS IN THE BASAL GANGLIA WHEN DOPAMINERGIC TONE IS ELEVATED

To obtain a neurodynamic basis for understanding the symptoms of psychosis, one needs information on changes in firing rate in the striatum and other nuclei of the basal ganglia when dopaminergic tone is elevated. Fewer studies investigate this than the converse situation of reduced dopamine tone, and there are no such studies in humans

or other primates. The best animal models for such studies are rats challenged with a single dose of amphetamine, and sometimes also sensitized to amphetamine by previous doses. In this model, the dose is of critical importance. In behavioral terms, low doses of amphetamine (~1 mg/kg) lead to locomotor hyperactivity. Larger doses (~5 mg/kg), used in some studies, produce initial locomotor hyperactivity, followed, at the height of the drug's action, by focused stereotyped sniffing, licking, gnawing, and head movements, from a fixed based, with no locomotor activity. Rats in this state are thought to be an equivalent of the florid psychotic state in humans, those affected by the lower dose, perhaps in a "prepsychotic state." A dose of 2 mg/kg is transitional between these two states, but if given to sensitized rats would have effects similar to 5 mg/kg in unsensitized rats. Since the lower-dose effects involve locomotion while the higher-dose ones involve smaller movements with suppression of whole-body movements, it is possible that the different effects could be interpreted, respectively, as increased activity in the direct versus the indirect pathway from the striatum.

9.3.1 Striatal Unit Firing in High-Dopamine States: Experiments and Theory

One study (Alloway and Rebec, 1983) has investigated the effect of a challenge dose of amphetamine on single-unit firing in the striatum, comparing control rats and those sensitized by 6 days of twice-per-day administration of amphetamine. The electrophysiological analysis was carried out in paralyzed rather than free-moving animals. Compared with rats given repeated saline injections, the sensitized animals showed greater excitation of neostriatal units in the first 30 min after the challenge dose of 1.0 or 5.0 mg/kg amphetamine. This is compatible with the view that proprioceptive cues that activate striatal units, have an enhanced effect in the stimulant-sensitized animal, as a result of an exaggerated synaptic reinforcement effect. It would be interesting to know if the same enhancement of excitation occurred in free-moving rats, but there are no such studies reported in sensitized animals.

A number of other studies of striatal unit activity have been reported in free-moving rats treated acutely with amphetamine. Basse-Tomusk and Rebec (1985) showed that cumulative doses of amphetamine (to a total of 2.0 mg/kg) produced increases and decreases of firing in similar proportions of neurons. Ryan et al. (1989) found that decreases were more common than increases, but the opposite was found by Haracz et al. (1989), Rebec et al. (1997), and Kish et al. (1999). The doses used in these studies range from 0.25 to 5.0 mg/kg, but the discrepancies cannot be explained on this basis. (In the study of Ryan et al., similar results were obtained for all doses between 0.5 and 5.0 mg/kg.) The study of Ryan et al. (1989) arguably gives the most reliable population data (with least sampling bias), since nearly half of the neurons studied were identified by their giving antidromic responses to SNR stimulation, and so would have included units which initially had no spontaneous activity.* However,

* Differences in sampling bias cannot explain the difference between studies: Units which were silent before the drug would have been identified by antidromic stimulation but ignored if identification was based on spontaneous activity. Since the only change in firing these units can show is an increase, detection of increases in firing would be favored by the method of Ryan et al. (1989) more than in other studies. However, the opposite result was actually found.

there was little difference in mean spontaneous firing rates between units identified in this way and other units. Whatever the exact distribution of units activated and suppressed by amphetamine, when increases in firing *do* occur, they are reported as quantitatively much larger (3- to 10-fold) than the decreases (mean of ~12% reduction) (Basse-Tomusk and Rebec, 1985; Haracz et al., 1989; Rebec et al., 1997).

Further behavioral detail is provided in some of these papers. Ryan et al. (1989) report that, in amphetamine-treated animals, when transitions occurred from pure locomotion to "locomotion plus stereotyped sniffing plus side-to-side head movement," 16/22 units showed further decreases in firing rate, 12 being completely silenced, but there were still 6/22 units where increase in firing occurred. In the transition from this state to the most severe signs of amphetamine intoxication ("in-place sniffing with stereotyped gnawing"), there were further decreases, 10/15 units being silenced, but there were still 4/15 units, which showed increased activity. Significantly, in several papers (Haracz et al., 1989; Rebec et al., 1991; Wang et al., 1992), it has been shown that striatal units, which, before the drug, showed increase of impulse activity in relation to body movements, showed enhanced movement-related activation after amphetamine. In such movement-related units, increase in impulse activity by the drug was seen more consistently than in non-motor-related units, where inhibition was more common. These associations do not arise because increases in striatal unit firing are a downstream consequence of drug-induced increase of movements: The increase occurs even when pre- and post-drug recording epochs are matched for the emitted behavior (Rebec, 1992; Haracz et al., 1993). Thus, the correlation appears to reflect a direct influence of the drug on striatal dynamics. As mentioned above, during the action of high-dose amphetamine (~5.0 mg/kg), locomotor activity appears first, followed, at the height of the drug's action, by focused stereotypy. Rebec et al. (1997) showed that units whose firing before the drug increased in relation to locomotion, showed further increase in the early phase of the drug's action when locomotion was increased. Those whose firing predrug increased in relation to sniffing/licking became most active at the height of the drug's action, when focused stereotypy predominated. Activation of movement-related unit firing also occurs with intrastriatal microinjections of amphetamine, but only in striatal regions closely linked to motor performance (Wang and Rebec, 1993). Again the increases, when they occur, are quantitatively much larger than the decreases.

These effects of increased dopaminergic tone on population distribution of firing rates of striatal neurons can be understood in part in terms of theory of function of the basal ganglia presented in Part I. Unit excitation related to bodily movement is likely to be driven by excitatory input from the cortex. Enhancement of such activity by amphetamine is then a manifestation of the role of dopamine in potentiating the cortico-striatal synaptic influences, which are already driving unit firing in a minority of neurons. (A similar effect was reported by Campbell et al. [2006]: Locomotor stimulation after intrastriatal microinjection of a D1 agonist was attenuated if an NMDA-antagonist was also infused.) The reduction in firing rate in the remaining majority of striatal neurons (notably those not related to locomotion) can then be seen as a reflection of local collateral inhibition produced by activated neurons on their neighbors. The selective increase in activity in movement-related striatal neurons is, thus, a very different phenomenon from the widespread increase in firing

rate in parkinsonian syndromes. There is also some evidence that different striatal units undergo increases in firing in the low- versus high-dose phases of amphetamine's actions. Whether the units whose increase in firing correlates with the small movements of focused stereotypy are really related more fundamentally with the suppression of locomotion which occurs at the same time cannot be determined. Thus, there is no clear evidence yet for a dissociation in firing rate changes compatible with proposed opposed roles in relation to the behavior for the cells of origin of direct versus indirect pathways. There is also no evidence *against* this proposal. The issue might be resolvable by careful combination of electrophysiological and ethological observations during behavior changes produced by a range of amphetamine doses.

A further possible effect of high-dopamine states on striatal unit firing should also be considered, based on the theory of action of dopamine. Normally, it is envisaged, impulse traffic in different axons in the cortico-striatal projection ranges from low to high. The high-activity axonal lines are supposed to carry potentially important signals, the terminals of which are candidates for synaptic potentiation. The low-activity lines are the ones reflecting ongoing cortical activity of less statistical significance, whose synaptic influence is either unchanged, or suppressed by synaptic depotentiation ("long-term depression": Reynolds and Wickens, 2002). The circumstances in which dopamine-mediated synaptic potentiation is envisaged to occur is a conjunction of three factors (Miller, 1981; Reynolds and Wickens, 2002; see Section 2.1): increased presynaptic activity, increased postsynaptic activity, and phasic dopamine release. Before synaptic strengthening occurs, the combined effect of these factors must reach some threshold level. If the phasic pulse of dopamine is abnormally large, or if dopamine release is more continuous than normal, the contribution of the other two factors needed to reach this threshold may be less than normal. In this circumstance the "cut-off" level of impulse activity in cortico-striatal axons, above which synaptic potentiation can occur will be lowered. The result is that synaptic potentiation may occur "accidentally," with respect to unimportant signals relayed from the cortex.

This shift in neuronal dynamics corresponds to a formulation of the abnormal information processing in high-dopamine states put forward 30 years ago (Miller, 1976). The relevant cerebral processing can be considered equivalent to an "associative machine," which takes as input a wide variety of signals, and is programmed to detect significant associations between any set of such signals. Referring to the striatum, and its role for behavior and cognition, the relevant associations are those between a pattern of input and those output strategies, which deliver motivationally favorable effects. In any such associational machine, there must be a "set point," somewhat similar to a probability criterion in an example of statistical inference. If this "set point" is fixed at a very rigorous level (e.g., "$p < 0.001$"), few associations will be detected, but they will be concluded very securely, with quite remote chance of error. If the set point is fixed at a much more lax level (e.g., "$p < 0.1$"), many more associations will be detected, many of which will correspond to correct associations, detected early, when evidence is not by any means overwhelming. However, some conclusions about associations will be reached which have no basis in reality, appearing as spurious, accidental conclusions. The shift to this lax state

of the associative machine can be translated, in real brain terms, as the result of an increase in dopaminergic tone in the striatum. The implication is that the signals which are reinforced and become influential in determining subsequent behavior or beliefs are not only "exaggerations and distortions" of real events and thoughts with motivational significance but some of them are also completely unrelated to reality, and can trigger behavior with no discernible goal, or give rise to beliefs with no discernible meaning or motivational value, even allowing for distortions of normal functions. This formulation will be referred to in the next section, dealing with phenomenology of psychosis. It is also relevant to some of the motor phenomenology of dyskinesias produced in high-dopamine states, discussed in Chapter 10. As a label for this pathology of information processing, we will henceforth use the term "adventitious reinforcement."

9.3.2 Unit Firing in Other Components of the Basal Ganglia in High-Dopamine States

A few studies also provide evidence on amphetamine-induced changes in impulse traffic in other structures of the basal ganglia. The evidence is fragmentary, and in some respects inconsistent. In reviewing these studies, it is best to start with the topic where conclusions can be made most clearly. This is the effect of amphetamine on firing in the pallidum (=GPe). Three papers using different methods give consistent indications that neural firing in the rat pallidum increases after amphetamine. Ossowska et al. (1984) showed that locomotor hyperactivity produced by 1.5 mg/kg amphetamine was largely eliminated if muscimol was microinjected into the pallidum, implying that the hyperactivity depended on increased impulse traffic in neurons of that nucleus. Bourdelais and Kalivas (1990) showed that extracellular GABA release in the ventral pallidum was reduced 40 min after administration of 2.0 mg/kg amphetamine, in parallel with locomotor activation. Such a reduction of an inhibitory influence is expected to be accompanied by increased impulse traffic in the postsynaptic neurons there. Tindell et al. (2005) show that unit activity in the ventral pallidum is increased in response to a conditioning stimulus in a conditioned reward paradigm, and the size of this increase is greater in rats administered an acute dose of amphetamine (2 mg/kg) in either naive animals or ones sensitized to amphetamine by pretreatment with escalating doses of the drug. However, 2 mg/kg given acutely in unsensitized animals outside the conditioning task *lowered* ventral pallidal firing rates from 11.35 to 7.78 impulses per second, and this dose produced no change in sensitized rats. To these three papers can be added that of Bergstrom et al. (1982) who showed, in paralyzed rats, that apomorphine (0.08–1.0 mg/kg) administered systemically causes a large increase in the rate of tonic neuronal firing in pallidal neurons. (Lower doses—20 or 50 μg/kg—expected to decrease dopamine release by action on autoreceptors had no effect on unit firing in pallidum.)

These pieces of evidence, pointing mainly to increased unit firing in the pallidum in high-dopamine states, can be accounted for in terms of the probable effect of the drug to cause (mainly) a reduction of striatal unit firing, with increases present in only a minority of projection cells (see Section 9.3.1). The particular striatal neurons

in which this reduction occurs are presumably those of the indirect pathway. If it is accepted that activity in these neurons is related to the suppression of active behavior, firing is likely to be reduced rather than activated when locomotor activity increases (mentioned in two of the above studies). The study of Tindell et al. (2005) does not report on concomitant behavior other than that of the conditioning task. It is thus uncertain whether the dose of 2 mg/kg elicited locomotor activity, or focused stereotypy from a fixed base. The latter would certainly be more likely in sensitized animals. If, in this experiment, this was also the result of this dose in unsensitized animals, one might expect it to be accompanied by increased firing in striatal units of the indirect pathway. This could then explain the discrepant result, a fall in unit firing in ventral pallidum when amphetamine is given outside the conditioning task. Again, combination of careful electrophysiological and behavioral observation of changes after various doses of stimulant is needed to clarify unresolved issues.

Downstream from GPe are the output nuclei of the basal ganglia (SNR and GPi). These receive inhibitory influences from both striatum and GPe. A few studies describe changes in unit activity in SNR of rats after administration of amphetamine. Kamata and Rebec (1985) studied unit firing response to a challenge dose of amphetamine, comparing control and stimulant-sensitized rats, in paralyzed preparations. In control animals (with saline pretreatment), the acute dose of amphetamine had little effect on firing rate in SNR, but in amphetamine-sensitized rats, there was a dose-dependent increase in firing rate, reaching 175% of control levels for a dose of 2 mg/kg. There were also rare units (whose proportion is not stated), which decreased firing in response to amphetamine, in control animals. Amphetamine pretreatment appeared to enhance such inhibitory responses as well as the excitatory ones (though a controlled comparison was not made). Three other studies report on the effects of single acute doses in free-moving rats. Olds (1988a) found that amphetamine (5 mg/kg) increased the mean unit firing rate in SNR from 24.2 ± 15.3 to 41.9 ± 31.3/s. Similar increases were reported for nondopaminergic neurons of the ventral tegmental area. No mention is made of whether any cells showing a decrease of firing rate. The increase occurred at the same time as bodily movements increased. Locomotion and stereotypy were not separated, but the former certainly was accompanied by increase in unit firing, and the increases in firing occurred for all doses between 1 and 5 mg/kg (Olds, 1988b). Gulley et al. (1999) reported that, before the drug, a large proportion of units (15/30) showed increases in firing related to movement, with increases by as much as 38%. Only 4/30 units showed decreases and 11 showed no change. After subcutaneous amphetamine, unit firing rate was drastically reduced regardless of its relation to behavior, by as much as 80–99%. In many units, the prevailing tonic activity was almost completely silenced. While there was no description of behavioral effects of the drug, the dose given (1 mg/kg) is likely to have produced locomotor activation rather than focused stereotypy. In another study (Waszczak et al., 2001), intrastriatal microinjections of amphetamine were used. Bilateral injections into the ventrolateral region were required before either behavior or unit firing in SNR was changed. The changes in unit firing (studied in parallel experiments in anesthetized or paralyzed preparations) were very heterogeneous, with the peak of behavioral activation being accompanied by a marginally significant net increase in firing. Changes in behavior consisted

of locomotion, sniffing, and oral movements, occurring together at the peak of the drug's response. It is possible that, in individual rats, either locomotion or stereotypy from a fixed based may have predominated.

To interpret such results, it has to be borne in mind that unit firing in SNR is not only under direct inhibitory control from the striatum, but also under indirect control from the striatum, via the pallidum (=GPe), which would lead to disinhibition when striatal input increased. Given this, the results of Gulley et al. (1999) in SNR are compatible with the model of basal ganglionic function proposed in Part I, although falling short of exact verification. In the undrugged rat, the few neurons in SNR whose firing rate decreased, probably correspond to those inhibited by the "direct" striatal output pathway, inhibited by the few activated striatal neurons. Their loss of tonic activity presumably leads to the release of specific pieces of behavior. The larger proportion that undergoes increase in activity can be attributed to loss of inhibition from other direct pathway striatal neurons subject to local inhibition from the few active neurons. The same mix of a minority of inhibited neurons and a majority of activated ones is seen in the stimulant-sensitized rat by Kamata and Rebec (1985), and the same explanation may apply. In any case, in the study of Gulley et al. (1999), amphetamine accentuated inhibitory effects on SNR units, presumably, both because activity in the few activated neurons of the direct pathway increase, and because unit activity in the pallidum was generally elevated, and transmitted greater inhibition to SNR. This is likely to be the cause of the general release of active behavior by the drug. In the study by Olds (1988a,b), the finding of a general *elevation* of firing rates in SNR after amphetamine is problematical. In empirical terms, it disagrees with the finding of Gulley et al. (1999). In theoretical terms, it could be explained by a predominant influence of the direct pathway, whose inhibitory influence is reduced due to lowered firing rates in the striatum. Reduction of such inhibitory influences might be expected if the high-dose syndrome (focused stereotypy from a fixed base) was produced by the drug. However, the same effects on SNR units were produced by low- as well as high-dose amphetamine. Thus, these results remain as an anomaly. The heterogeneous mix of excitation and inhibition seen by Waszczak et al. (2001) cannot be given a precise account, but the tendency toward increase in firing at the peak of the behavioral activation may reflect the fact that there was some focused stereotypy, generally occurring from a fixed body position, rather than during locomotion. This would have favored activity in the indirect pathway, disinhibiting SNR.

The changes in firing rate in either the striatum or SNR are likely to be a consequence of dopamine-mediated enhancement of excitatory synaptic transmission in the striatum. It is very likely that similar changes occur in the basal ganglia in humans, during states of psychosis, and are presumably the cause of the psychotic symptoms. A major contradiction arises here in relating the changes in firing seen in animals to the cognitive and behavioral changes seen in humans during psychotic states: It is well documented that the reinforcing actions of dopamine and the dopamine-mediated synaptic changes upon which they depend are produced mainly by activation at the dopamine D1 receptor (Calabresi et al., 2000; Kerr and Wickens, 2001; see discussion in Section 2.1). However, drug therapy of psychotic states in humans depends on blockade at D2 receptors, not D1 receptors. We return to this severe paradox later in this chapter.

9.4 OVERACTIVITY OF STRIATAL DOPAMINE IN RELATION TO THE SYMPTOMS OF PSYCHOSIS

This account of disturbed neurodynamics in animal models of psychosis, albeit somewhat sketchy, helps one to understand psychological features of the psychotic state, and, in a few instances, to make predictions that go beyond what is established.

Dopaminergic tone is normally influenced by the motivational significance of concurrent external events or internal neural activity. One would then expect that mental images with motivational significance should be reinforced excessively in high-dopamine states. Dopaminergic reinforcement has generally been taken to apply to events of positive motivational valence (as indicated by use of the term "reward"). However, there is increasing evidence from animals that dopamine is related to motivational significance more generally, including events with negative as well as positive valence (Killcross et al., 1997; Wickelgren, 1997; Gray et al., 1997; Levita et al., 2002). This principle is likely to be important in understanding the symptoms of psychosis.

9.4.1 Perceptual and Conceptual Bases of Psychotic Symptoms

In humans experiencing psychotic states, overactive reinforcement applies most obviously to perceptual or conceptual images. With regard to the *perceptual* images, this description applies to two classes of experience. *Illusions* occur, especially in the early stages of a psychotic episode, in which sights and sounds appear more vivid, more attractive or aversive, and more memorable than normal. This is captured well in the following quotation:

> On several occasions my eyes became markedly oversensitive to light. Ordinary colors appeared much too bright, and sunlight seemed dazzling in intensity ... My capacities for esthetic appreciation and heightened sensory receptiveness ... were very keen at this time. (Anon-1, 1955.)

A similar enhancement of perceptual impressions is also mentioned by Rylander (1972) in amphetamine-intoxicated humans. ("The perceptions of all senses are sharpened and partially changed.") In addition, in endogenous psychoses, many trains of thought, while not in themselves experienced in the perceptual domain, have associations with subliminal perceptual images. *Hallucinations* in psychosis when dopaminergic reinforcement is enhanced can then be seen as an amplification of these subliminal images. This occurs to the point where they are experienced as perceptions of external origin, clinically recognizable as hallucinations.

> I ... began to have visual hallucinations, in which people changed to different characters, the change indicating to me their moral value. ... Another type of visual hallucination I had at this time was exemplified by an occurrence during a family trip through Utah: The cliffs along the side of the road took on a human appearance and I perceived them as women, bedraggled and weeping. (Anon-2, 1992, with permission from Oxford University Press.)

Illusions and hallucinations are generally regarded as psychopathology in the perceptual domain. However, in so far as they involve exaggeration of motivational

significance, they can guide overt behavior, or determine the focus of attention. They, thus, fall within the scope of the present theory of the basal ganglia, as involved in behavioral and attentional selection.

With regard to *conceptual* images, those with the potential to guide complex behavior have intrinsic motivational significance and can be identified as "beliefs." In so far as they have motivational components, they should be acquired, like other motivationally significant behavioral programs, by dopamine-mediated reinforcement directed at the striatum. Exaggeration of the positive and negative motivational significance of beliefs would then give them one of the characteristics of psychotic delusions. In addition, these delusions are often described as "incorrigible," that is, patients in an active delusional state cannot be persuaded of the falsity of their beliefs by any amount of rational argument or empirical evidence. This further characteristic of psychotic delusions is what would be expected if the dopaminergic reinforcement mechanism by which beliefs are acquired is excessively strong.

The subject matter of psychotic delusions—again quite characteristic of dopamine-mediated psychosis—can vary widely. A detailed account of the ways in which overactivity of dopaminergic processes leads to delusions with their distinctive detailed content has been given by Miller (1993) and Chouinard and Miller (1999a,b). In these accounts, delusions are divided into three broad types. In the first, there is an exaggeration of basic "visceral" motives, leading to delusions of wealth, fame, love, sex, pregnancy, etc. The second class of delusion arises from exaggeration of what may be called "cognitive motives," namely, the attractiveness of mental images that are in some way "interesting" or "novel." A particular type of such cognitive attractiveness occurs when a mental image (an "idea") comes to mind, which might be seen as providing an "explanation." When such attractiveness is abnormally exaggerated it may lead to delusions based around systems of ideas in philosophy, religion, or politics, and delusions about topics such as telepathy, the occult, and space invaders. Any of these ideas can then be elaborated as focal points for "explanatory" aspects of delusional systems. In part, this is because these ideas are rich in associations or symbolism, and so are fertile ground for delusional elaboration when normal logical constraints are relaxed. The third class of delusions are on "unpleasant" themes, including delusions of persecution, deception, and impending disaster. While these may be generated and sustained in part because they are "interesting" and provide "explanations" (as in the second class of delusion), they may also reflect exaggeration of images with negative motivational valence, and are no doubt colored by unpleasant real events in a person's life at the time they are becoming unwell.

To these three classes of psychotic delusion, a fourth can tentatively be added, based on the theory developed above: In Section 9.3.1, it was suggested that, in high-dopamine states, synaptic potentiation in the striatum may occur for terminals with levels of impulse activity distinguished from background levels less sharply than under normal circumstances. The information represented by such activity would then be the target of "adventitious reinforcement." In psychotic states in humans, this might correspond to some examples of a category of delusion referred to as "bizarre delusions," although this is not very well defined (Tanenberg-Karant et al., 1995), and corresponds in part to classes of delusions already mentioned. An example

(from Mullen, 2003) is the belief that "one's neighbors are stealing electricity and food through the walls." This does not seem to be an exaggeration or distortion of ideas with "motivational significance." Such psychotic delusions may reflect real errors in the associative machine, arising when too lax a criterion for acceptance of a significant association prevails in the striatum.

The paranoid psychosis induced by amphetamine is basically similar to the description just given for endogenous psychoses. However, some symptoms characteristic of schizophrenic psychoses (the so-called "passivity" symptoms emphasized in the psychopathology of Kurt Schneider), which respond only partially to antipsychotic drug treatment (Cloninger et al., 1985; Harrow et al., 1987), are reported to occur less frequently in cocaine psychosis (Rosse et al., 1994), and are likely to be less dependent on dopamine overactivity.

Most of the symptoms of psychosis are not meaningless images but are organized in a manner bearing some resemblance to normal experiences. Although exaggerated and distorted, they have sharp subjective definition. Correspondingly, one would not expect a tendency for CTH assemblies to fuse, as is the case in Parkinson's disease. Instead, cues which can control behavior should become more distinctive or salient than normal, and, if more than one occurs at the same time, there should be vigorous competition between them (strong selective attention), yet keeping each distinct and separate. Studying this topic in humans is difficult because of an important confound: Subjects who become actively psychotic are usually those where the psychosis is a complication of an underlying more protracted disorder, usually schizophrenia. Apart from the practical difficulties of doing complex psychological experiments in actively psychotic subjects, this underlying schizophrenic disorder has its own impairments in selective attention, which are enduring traits additional to features characteristic of psychosis. No studies have been published which selectively examine the detailed attentional abnormalities specific to psychosis in such patients. However, there is a body of evidence analyzing the attentional abnormalities in experimental animals under the influence of stimulants. This has been reviewed by Miller (1993). In contrast to Parkinson's disease, discrimination learning is accelerated, and so is reversal of discrimination. There is no suggestion of a tendency to fusion of the normally separate representations of different stimuli, but rather there is an "acquired distinctiveness of cues." In addition, cues that are irrelevant to task performance may retain an abnormal ability to control behavior. As a summary, Miller (1993) uses the phrase "unresolved rivalry between competitors" to describe the stimulant-induced changes in selective attention, a process very different from that in parkinsonian syndromes.*

If dopamine-mediated psychosis is due to an exaggeration of the reinforcement function of dopamine, there should be a recognizable phase of "acquisition" of the exaggerated versions of mental images (analogous to the learning phase in

* Since, in theory, the neurodynamics of the basal ganglia and CTH network in psychosis are in some ways the converse of those in Parkinson's disease, predictions might be made, based on experimental designs similar to those reviewed in Section 8.2: However, complex psychological tests are probably precluded in actively psychotic patients. Designs using TMS to assess the strength of inhibitory processes in the cortex might be more feasible, but raise ethical problems in patients who may have delusions about thought control.

instrumental conditioning). This may not be evident for symptoms such as hallucinations, which, inherently, are "immediate experiences," not persisting in memory. However, *beliefs* are normally acquired gradually over a period of time and persist as memories or habits that may guide behavior. The same should be true of delusional beliefs. Correspondingly, it is well documented clinically that delusions often start off in relatively simple form, but become progressively elaborated, sometimes into all-encompassing systems of belief. This process is captured well in the following excerpt:

> Over a period of several months, I began to believe that messages were being left for me in graffiti across the campus. I also began to believe that my phone was being tapped. ... One afternoon I realized that the people on the radio were talking to me, much as one has an intuition about a geometry proof, a sudden dawning of clarity and understanding. This clarity was more compelling than reality ... As time passed I became proficient at reading code ... I learned to communicate by deciphering bits of conversation, reading newspaper articles and listening to songs on the radio. (Weiner, 2003, with permission of Oxford University Press.)

Sometimes the elaboration of delusions occurs at a pace much faster than the acquisition of normal beliefs.

> My own tendency to day-dream indicates that my imagination could easily be separated from the selective processes which tend to control it, in matters of practical decision making. But in the new state of mind I was now in, the selection process was scarcely operating at all, with the result that I connected everything up together, sometimes at phenomenal speed. (Miller, 2000a, reprinted with permission.)

This acquisition phase can be brought to a halt by dopamine-blocking antipsychotic drugs. Nevertheless, once acquired, the exaggerated and distorted beliefs referred to as delusions should be as persistent as any other beliefs, despite continuation of the antipsychotic drugs. This principle explains a feature of therapy with antipsychotic drugs, which is paradoxical in more straightforward accounts of the dopamine hypothesis. This is the long time course of recovery during such therapy. The full extent of the therapeutic process produced by antipsychotic drugs is achieved slowly, over weeks or longer, although the relevant dopamine receptors are blocked within a few hours (Casey et al., 1960; Cole and Davis, 1969; Davis and Garver, 1978; Crow et al., 1980). The slow development of the benefit from antipsychotic drugs applies to treatment not only with classical neuroleptic drugs, but also to that with atypical antipsychotic drugs (Lieberman et al., 1994; Honer et al., 1995).

The psychological model of psychosis, based on concepts of dopamine-mediated learning, has been developed in several previous publications (Miller, 1976, 1984, 1987, 1993; Chouinard and Miller, 1999a,b). It is proposed that the medications, rather than abolishing psychotic symptoms "at a stroke," reduce the pressure from newly forming beliefs, and thus, allow the rest of a person's cognitive apparatus to engage in restorative activity to resolve the conflicts of beliefs set up during the period of active psychosis. This is captured in the following account:

> Gradually, the spate of my thoughts subsided; and though my mind did not flow exactly along the old channels, it was roughly constrained within the banks of normality,

> rather than dispersed over a wide flood plain. ... Talking once to the professor*, I mentioned that almost all my previous strange ideas had receded in my mind except for the idea that I was somehow possessed of mysterious telepathic powers, or precognitive insights. He argued against the theory, in general terms, but it continued to concern me. (Miller, 2000a, reprinted with permission.)

In terms of learning theory this could be called "extinction." In more psychodynamic terms, one would refer to this as the "working through" conflicts of belief arising during the period of active illness. During such "working through," the person actively compares current beliefs with past memories and each day's new experiences. Whether and how completely this process can take place depends on factors other than those that led to the state of active psychosis. These factors include the duration of psychosis before drug treatment was initiated: Long periods of untreated psychosis resolve more slowly than acute episodes receiving treatment quickly. This is familiar in clinical practice, and is documented more objectively in studies of Axelsson and Ohman (1987), McDermott et al. (1991), and Loebel et al. (1992). Baseline personality may also determine whether and how completely a person can adapt and modify strongly held delusional beliefs. For instance, Fenton and McGlashan (1986) showed that if schizophrenia occurs in patients with obsessive/compulsive symptoms, the prognosis for the psychotic illness is then bad. In some cases, low-grade psychotic symptoms persist long after the period of active psychosis, and despite otherwise effective drug therapy. This may be a reflection of relative rigidity in the cognitive handling of belief structures whether or not they are delusional, as a basic personality feature independent of the illness.

A prediction from this model of psychosis is that the specific content of psychotic delusions should have a tendency to persist from one episode to another. There is little published data on this topic. However, one autobiographical account clearly supports the prediction. Vonnegut (1975) in "*The Eden Express*" describes two psychotic breakdowns, related to the use of hallucinogens and stimulants. These possibly occurred in a subject with a predisposition to psychotic illness. The two episodes are separated by a period of 3–4 weeks, during the first of which there was hospital treatment when neuroleptic drugs were prescribed. The second episode continued many of the delusional themes of the first, with some new elements. A scientific report on this topic (Sinha and Chaturvedi, 1989) investigates persistence of delusional content across successive episodes. This occurred in one-third of their psychotic patients. Such continuity of content between episodes would be expected if delusional beliefs are stored in memory, lie dormant during remission, but "reawaken" if the conditions for psychosis return. The study of Sinha and Chaturvedi (1989) suggests an explicit test of the hypothesis that memory mechanisms are recruited in psychotic states, and are important in the persistence of delusions. It is predicted that the shorter the interval between the episodes, the greater the continuity between episodes of the delusional content. This would not be expected if continuity had other determinants (e.g., cultural factors). In a personal communication with Drs. Sinha and Chaturvedi,

* The late Professor Charles Phillips, who gave the author much help and support during this period of illness in 1973.

the present author was informed that, for patients with affective psychosis, when there was continuity of delusional content, the mean interval between episodes (1.13 years) was significantly shorter than when there was no continuity of content (5.4 years) ($p < 0.05$). Curiously, such a difference was not shown for the group of patients with schizophrenia in this study.

An alternative explanation of the long time course of therapy with antipsychotic drugs has been advocated by Grace and Bunney. Experiments in rats (Bunney and Grace, 1978; Grace and Bunney, 1986; Grace et al., 1997) have shown that, after prolonged regimes of antipsychotic drugs, the tonic firing of midbrain dopamine neurons may cease, a phenomenon referred to as "depolarization block." Moore et al. (1998) showed that the presence of depolarization block determined by electrophysiological methods correlates with the reduction of extracellular dopamine levels in the striatum, as determined by microdialysis. Since depolarization block is seen only when neuroleptic drugs are administered for at least a few weeks, it has been proposed that a similar process could be the cause of the slow recovery from psychosis during drug treatment (Chiodo and Bunney, 1983; Grace and Bunney, 1986). There is no reason to doubt the basic finding of depolarization inactivation. However, there are strong reasons for doubting its applicability to the clinical fact of slow recovery during antipsychotic drug treatment. The basic electrophysiological finding in animals has generally been seen in rats anesthetized with chloral hydrate. Occasionally, depolarization block after chronic regimes of antipsychotic drugs has been shown in paralyzed preparations (Chiodo and Bunney, 1985), but other reports have failed to find the effect in such preparations (Mereu et al., 1994, 1995; Melis et al., 1998). Depolarization block may thus be a phenomenon arising from the combined effects of anesthesia and previous chronic regimes of antipsychotic drugs. Two other techniques for assessing dopamine tone support this conclusion. Dopamine release in the striatum can be measured with dialysis probes or *in vivo* voltammetry. After chronic regimes of neuroleptics, there is a massive reduction in dopamine release if the test is done in anesthetized animals (Blaha and Lane, 1987; Lane and Blaha, 1987; Ichikawa and Meltzer, 1990; but see Moghaddam and Bunney, 1993). However, dopamine release is not drastically reduced in such drug-treated animals if the final test is done in the free-moving state (Zhang et al., 1989; Hernandez and Hoebel, 1989; Moghaddam and Bunney, 1993). In addition, after chronic regimes of neuroleptic drugs, dopamine release can still be activated in free-moving rats by mild stress or by electrical stimulation of the prefrontal cortex (Klitenick et al., 1996), findings incompatible with the idea that depolarization block occurs in such animals. A further method of assessing dopamine release is to measure levels of the metabolite 3-methoxytyramine. Unlike other dopamine metabolites, this is produced by an enzyme present only in the postsynaptic neurons, and levels of this metabolite are thus a direct measure of released dopamine (rather than that originating in part in presynaptic neurons). This metabolite can be assessed in free-moving animals (killed by rapid microwave irradiation). According to Chrapusta et al. (1993; see also Egan et al., 1996a), 3-methoxytyramine levels at the end of a chronic regime of neuroleptics are similar to those in control animals, suggesting again that in unanesthetized animals, dopamine release is not markedly reduced. Thus, the depolarization block hypothesis is unlikely to apply to either unanesthetized animals, or to humans

treated with antipsychotic drugs. In any case, this hypothesis provides no account of the details of the phenomenology of psychosis, or of the active process of "working through" during recovery from psychosis, and the relation between rate of recovery and duration of untreated psychosis.

In the previous subsection, the tentative conclusion was reached that, in high-dopamine states, a small proportion of striatal neurons undergo increases in impulse activity. The overactivity of these few neurons could apply to neurons of origin of either the direct or the indirect pathway. One would anticipate that the former would lead to "positive" symptoms, featuring in the above discussion, and representing abnormal *exaggeration* of normal function and experience. These are inherently more likely to attract the attention of clinicians than those arising from overactivity in the neurons of origin of the indirect pathway. For the latter, one would expect that abnormal *suppression* of normal functions would occur. This could consist of sudden cessation of a train of thought. Something like this does occur in schizophrenia, but a distinction needs to be made between true cessation of a train of thought and derailment of thought by other competing trains of thought. If this occurs in the manner suggested, it should not be a result of competition from other concurrent foci of mental activity. Such a description fits one of the symptoms of schizophrenia, referred to as "thought blocking" or "thought withdrawal." There has, however, been little detailed examination of this symptom, and Wing et al. (1974) consider it to be very rare. Before it can be attributed to excessive activity in neurons of origin of the indirect pathway, in dopamine-mediated psychosis, questions need to be answered: Is this symptom characteristic just of the psychotic state, rather than being an enduring trait in schizophrenia? Is it characteristic of stimulant-induced psychosis, and brought under control by administration of antipsychotic drugs?

These questions do not yet have a clear answer. In factor analyses of symptoms of schizophrenia, the symptoms called "blocking" or "thought withdrawal" tend to load on the same factor as other "positive symptoms" ("reality distortion"), rather than on factors related to traits of the disorder ("psychomotor poverty," or "disorganization" factors) (Silver et al., 1993; Cardno et al., 1996; Emsley et al., 2001). Thus, they may be true psychotic symptoms, covered by the present account of psychosis, rather than traits of schizophrenia. However, more detailed factor analyses find that thought withdrawal loads with the same factor as "first rank delusions," but not with the more usual psychotic delusions (Kimhy et al., 2005). In addition, thought withdrawal is more common in schizophrenic psychoses than in cocaine-induced psychosis (dopamine overactivity uncomplicated by additional trait aspects of schizophrenia) (Rosse et al., 1994). This suggests that thought withdrawal is not a primary symptom of dopamine-mediated psychosis.

A further possible indication that some of the symptoms of active psychosis reflect overactivity in neurons of origin of the indirect pathway is that the so-called negative symptoms (as well as the classic positive ones) may be attenuated by treatment with antipsychotic drugs (Meltzer et al., 1986; Breier et al., 1987; Kay and Singh, 1989; Schuepbach et al., 2002), and sometimes the changes in negative and positive symptoms are reported to occur in correlation (Czobor and Volavka, 1996). This is not often reported, probably because any amelioration of negative symptoms may be offset by behavioral suppression or sedation produced by medications, and

in any case may be combined with enduring negative-symptom traits, essential to schizophrenia, rather than to the psychotic episode. A more detailed study of this is required.

9.4.2 Behavioral and Motor Bases of Psychotic Symptoms

The symptoms discussed above are mainly in the cognitive domain rather than the behavioral or motor domains. This suggests that they arise due to dopamine activity in the caudate nucleus rather than the motor region of the striatum, the putamen, a suggestion for which there is some evidence (see Section 9.2). However, during intoxication with amphetamine, it is likely that excessive dopamine release occurs from dopamine terminals in all parts of the striatum. In this situation, one might expect symptoms to emerge in motor and behavioral domains (aka "macro- and microbehavior") as well as the typical symptoms of psychosis. In the behavioral domain, this is well documented in the account of severe amphetamine or cocaine intoxication in humans by Rylander (1972) and Schiorring (1981). Rylander's account, dealing with symptoms seen after large-dose intravenous administration of amphetamine, describes obsessive repetition of acts in the person's normal repertoire, referred to by the Swedish addicts in this study as "punding." This occurs in the vast majority of subjects who have abused amphetamine in this way for a period of time (Rylander, 1972). The details of such stereotyped behavior is characteristic of the individual, in ways to be expected from their social lives. For instance, there are differences in the punding behavior performed by men and women, according to their social roles. In men, it might involve manipulation with technical equipment (radios, watches, engines), while in women it could involve incessant tidying, hair combing, or nail polishing. Punding has also been described in parkinsonian patients receiving L-DOPA (Friedman, 1994). Punding is characterized as "an intense fascination with repetitive purposeless movements, such as taking apart mechanical objects, handling common objects as if they were new and entertaining, picking at oneself without stop, etc." (Friedman, 1994). Despite its characterization as "purposeless," such behavior can be seen as repeated fragments of purposeful behavior. Rylander comments that these are acts which the person normally likes to do, and, in the abnormal situation of intoxication, are performed with some subjective pleasure. While not automatic or involuntary, these acts are often performed to the complete neglect of other activities, which would normally require attention. These observations imply that such "punding" is sustained by overactive reinforcement, as is hypothetically the case, in the cognitive domain, for incorrigible delusions. It is not a simple acute pharmacological effect, but evolves progressively during the period of intoxication (Ellinwood et al., 1973), and in some subjects lasts for days after a single injection (Rylander, 1972). In these temporal aspects, punding resembles the delusions of endogenous psychosis. It has been suggested that punding represents a pathology of normal dopaminergic reinforcement mechanisms, with increasing focus on ever-narrowing patterns of activity (Ridley and Baker, 1982). Rylander also draws attention to the similarity between "punding" and the stereotyped behavior seen in animals when intoxicated with stimulants. Although cross-species comparisons should be made cautiously, stereotypies after amphetamine are well known in

monkeys (Ridely and Baker, 1982) and rats (Randrup and Munkvad, 1965), and have generally been regarded as similar phenomena to those seen in humans. Ellinwood (1971) refers to the mechanisms involved as "accidental conditioning."

In the motor domain, Rylander (1972) also describes stereotyped automatic unwilled jerking movements of face, arms, and legs (see also Ashcroft et al., 1965; Mattson and Calverley, 1968). These movements consist of teeth grinding, tongue movements, lip smacking, grimacing, twisting of head and neck, and choreoathetoid movements of the limbs. Rylander uses the term "choreiform" to describe these movements, but it is not established that these movements are similar to those of Huntington's chorea. The latter are described as random (see Chapter 7). However, if the movements seen by Rylander during amphetamine intoxication reflect overactive dopaminergic reinforcement, one would expect them to constitute distinct patterns, characteristic for each person, and sustained over time. Rylander's account does not provide such detail, but does mention one person in whom the abnormal movements persisted for several weeks after the last drug injection. This is consistent with the movements having been acquired and then sustained by some sort of "memory" effect, in a manner similar to the persistence of psychotic delusions. L-DOPA, which also increases dopamine activity, has usually been found not to produce abnormal movements in humans without preexisting Parkinson's disease (Mena et al., 1970; Arts et al., 1991; Rajput et al., 1997) or in normal animals (Ng et al., 1973; Sax et al., 1973; Boyce et al., 1990b; Alexander et al., 1993). However, some studies report abnormal movements in normal monkeys after high doses were given intravenously (Mones, 1972; Sassin et al., 1972) or by IP injection (Sassin, 1975), especially if central actions were potentiated with a peripheral decarboxylase inhibitor (Mones, 1973). Mones et al. (1973) also saw dyskinesias in normal monkeys given high doses of L-DOPA as an IP injection, but the symptom emerged only after the second of the two injections. More recently, in experiments in normal monkeys given twice-daily injections of much lower doses of L-DOPA, abnormal limb movements have been reported (Togasaki et al., 2001), described as "choreoathetoid." Consistent with their being acquired by a process of overactive reinforcement, their intensity increased over the first few days of administration, and was generally more severe for the second dose each day (4 hours after the first). Rylander's description of the abnormal movements gives little indication that they are fragments of once-purposeful behavior. Instead, it is probable that they reflect the process of "adventitious conditioning," suggested in Section 9.3.1, on theoretical grounds, where signals of relatively low intrinsic significance can become targets of dopaminergic reinforcement.

It needs to be stressed here that the abnormal movements reported by Rylander in addicts self-administering amphetamine are seldom reported in the literature on the effects of amphetamine in humans. The basic mechanisms by which amphetamine releases dopamine is by promoting "reverse transport" of the transmitter sequestered in dopaminergic terminals. After repeated doses, this process is supplemented by conditioning processes, which increase impulse-associated transmitter release. Rylander's subjects were administering the drug by an intravenous method, which, by the first of these processes, was likely to produce extremely high levels of extracellular dopamine, which would seldom be attained in more usual ways of amphetamine administration. Likewise, the production of dyskinesias by IV or IP

injection of L-DOPA in normal monkeys is a more potent means of dopaminergic stimulation than is achieved in usual treatment in humans. The implication is that, production of such abnormal movements in normal humans or animals generally requires extreme dopaminergic stimulation. This conclusion becomes relevant in Chapter 10, in understanding the dyskinesias sometimes associated with L-DOPA treatments in Parkinson's disease. This symptom usually occurs in humans only in the special circumstances of L-DOPA treatment in advanced stages of the disease. In Chapter 10, it will be argued that changes in the striatum occur in these advanced stages which make L-DOPA able to have unusually potent dopaminergic effects, which may be similar to amphetamine in the study of Rylander, or IV or IP injection of L-DOPA in monkeys.

9.5 PHARMACOLOGY OF PSYCHOSIS

It is widely accepted that the dopamine receptor type whose blockade by traditional neuroleptic drugs determines therapy for psychosis with these drugs is the D2 receptor family. This conclusion is based on the fact that, for a range of such drugs, clinical potency runs generally in parallel with their affinity for the D2 receptor, but not with that for the D1 receptor (Creese et al., 1976; Seeman, 1980, 1987). However, this raises problems for the theory of dopamine-mediated psychosis outlined above: In the development of these drugs, many psychopharmacological tests on animals have been used. Tests involving blockade of instrumental learning (such as conditioned avoidance) are better predictors of the potency of an antipsychotic drug than are tests based on the motor effects of neuroleptic drugs. Specifically, the clinical potency of atypical drugs (such as clozapine and thioridazine) is predicted well by their potency in blocking learning tasks, while tests based on motor effects predict that these drugs would have lower therapeutic potency than is actually the case (Miller, 1987; Miller et al., 1990). The close relation between learning tasks studied in animals and the therapeutic effects of antipsychotic drugs in humans supports the theory of psychosis presented above, based on psychological actions of dopamine on reinforcement and its physiological actions in synaptic potentiation. However, the receptor type on which dopamine-mediated reinforcement and synaptic potentiation depends is the D1 (or D1-like) receptor, not the D2 (or D2-like) receptor (see Section 2.1).

Thus, there appears to be a major paradox surrounding the receptor-type mediating therapy with antipsychotic drugs: Solid evidence shows that antipsychotic drugs act by blockade of dopamine D2 not D1 receptors. Clinical trials of D1-blocking agents have been conducted (Gessa et al., 1991; De Beaurepaire et al., 1995; Den Boer et al., 1995; Karlsson et al., 1995a,b; Karle et al., 1995), and are regarded as showing that these drugs have no antipsychotic effect. Nevertheless, on the basis of much evidence, the basic processes of learning and synaptic modification underlying active psychosis appear to involve the actions of dopamine at D1 more than at D2 receptors.

Other evidence adds to this paradox. When dopamine receptor occupancy by antipsychotic drugs is measured (using PET), D2 occupancy with several typical neuroleptic drugs prescribed in standard therapeutic doses is similar at 65–80% (Wiesel et al., 1990; Farde et al., 1992; Nordström et al., 1995). When the dose

required to produce 75% receptor occupancy is plotted against the clinically effective dose, the points for all antipsychotic drugs, including the newer "serotonin–dopamine antagonists" fall roughly on a straight line. However, there is a single exception—clozapine—for which clinically effective doses produce an occupancy much less than 75% (Farde et al., 1992; Nordström et al., 1995; Nyberg et al., 1996). Clozapine is not only an effective antipsychotic agent, but, fortunately, is effective in many patients who fail to respond to other antipsychotic medications. This indicates that receptors other than the D2 receptors may be involved in psychosis and antipsychotic therapy.

How can this paradox be resolved? A significant point is that there appears to be some form of interaction between dopamine D1 and D2 receptors. Some of this evidence suggest intracellular interaction of the effects of the two receptor types, but there is no consensus about the nature of such interactions (i.e., whether synergistic or antagonistic). A more consistent body of information documents interaction at the behavioral level. This evidence shows that D1 and D2 receptors act synergistically on behavior, notwithstanding the evidence that the D1 receptors are more closely linked to the reinforcement function than the D2 receptors. For instance, behavioral effects produced by D2 agonists can be prevented if dopamine synthesis or release is blocked (Johnson et al., 1976; Braun and Chase, 1986; Arnt et al., 1987; Longoni et al., 1987a,b; Walters et al., 1987). This suggests that concurrent activation of a dopamine receptor additional to the D2 receptor is required before the behavioral effect is shown. Some studies show specifically that the receptor at which this additional stimulation is needed is the D1 receptor (Pugh et al., 1985; Molloy et al., 1986). This is corroborated by evidence that D1-selective antagonists can attenuate some of the behavior-activating effects produced by D2-selective agonists (Molloy et al., 1986; Longoni et al., 1987b). Notable among this evidence is the study by McQuade et al. (1992), which compared a wide range of dopamine-blocking drugs in their reduction of conditioned avoidance responding, the behavioral test in animals most closely related to antipsychotic effects in humans. It was found that, for drugs, which, in absolute terms had a higher affinity for D1 than D2 receptors, there was a linear correlation between D1 affinity and avoidance blocking potency. Similarly, for drugs, which, in absolute terms had a higher affinity for D2 than D1 receptors, there was a linear correlation between D2 affinity and avoidance blocking potency. These results indicate that, in principle, blockade at either dopamine receptor type can determine the vigor of avoidance responding in rats. Presumably, the same principle may apply to the antipsychotic effect in humans. However, very few antipsychotic agents in regular clinical use have greater affinity at D1 than D2 receptors. Thus, it is understandable that the correlation between receptor affinity and clinical potency that has been established is with affinity for D2 rather than D1 receptors. If blockade of *either* receptor type is clinically effective, correlation between clinical potency and D1 receptor affinity might easily have been missed. The single commonly used antipsychotic drug known to have somewhat higher affinity at D1 than D2 receptors—clozapine—has remarkable therapeutic properties, superior in some ways to classical antipsychotic drugs. These properties have not yet been satisfactorily explained. However, the pharmacology of clozapine is very complex, and a number of hypotheses for its special action are viable.

To resolve the paradox, a suggestion has been made in several papers (Miller et al., 1990; Miller and Chouinard, 1993; Miller, 1997) that D2 blockers can act to attenuate the reinforcement/incentive function of dopamine by an indirect rather than a direct action, the final target of their effect being the D1 receptors and the intracellular production of cAMP. Specifically, it was noted that the motor side effects, which D2 blockers produce have a negative motivational valence. Since the midbrain dopamine neurons were supposed to respond to positive-going motivational events, it was proposed that, by unspecified pathways, the motor side effects were accompanied by slowing the firing or reduction in burst firing in the dopamine cells. If this were to be the case, D2-blocking neuroleptic drugs would reduce dopamine release in the striatum, and so could "unload" the transmitter bound to the D1 receptors, hypothetically important ultimately for antipsychotic actions. This hypothesis is depicted in Figure 9.2 (left side).

There are two arguments against this hypothesis: First, if the production of motor side effects were a necessary mediating stage in producing antipsychotic effects of neuroleptic drugs, use of anticholinergic agents to reduce these side effects should completely undo the therapeutic benefit from the medications. While there is evidence that anticholinergic agents may slow the course of therapy (Singh and Kay, 1973, 1978, 1979; Singh et al., 1987), they do not completely *prevent* therapy with D2-blocking drugs. Second, D2 blockers have usually been said to accelerate, rather than reduce the firing of the midbrain dopamine cells. However, this statement is based on experiments in anesthetized or paralyzed rats. Acceleration of firing after D2 blockers has not been shown in free-moving animals, which are most relevant to the situation of human therapy. B.I. Hyland et al. (pers. com.) have recently succeeded in recording from dopamine neurons in free-moving rats. In this exacting experiment, they showed that neuroleptic drugs *do not* slow dopamine neuron firing, nor do they reduce burst firing. This is a decisive refutation of the original hypothesis of Miller and collaborators (Figure 9.1).

There is however an alternative way in which D2 blockers could act indirectly to reduce cAMP formation in the striatum, involving cholinergic mechanisms. Acetylcholine has important functions in the striatum, arising from a population of cholinergic interneurons there (DiFiglia, 1987). These neurons are normally tonically active, but this activity is inhibited by dopamine release, acting at dopamine D2 receptors (Herrting et al., 1980; Stoof et al., 1982, 1987; Scatton, 1982; Lehmann and Lange, 1983; Wong et al., 1983). Therefore, it is likely that administration of D2-blocking neuroleptic drugs lifts the inhibition on these neurons, and raises firing rates, with the result that ACh release in the striatum increases. Since the extrapyramidal motor side effects produced by these drugs can be alleviated by anticholinergic drugs, it is likely that these side effects are the result of such excessive ACh release.

There are at least five muscarinic receptor types in the striatum (Bonner et al., 1987; Wei et al., 1994). Their exact role is still not yet resolved. However, of relevance here are the so-called M2 and M4 muscarinic receptors, whose cytological distribution in the striatum is described by Hersch et al. (1994). The M2 receptors appear to be involved in the production of motor side effects, to judge from behavioral experiments in mice in which the gene for these receptors is deleted

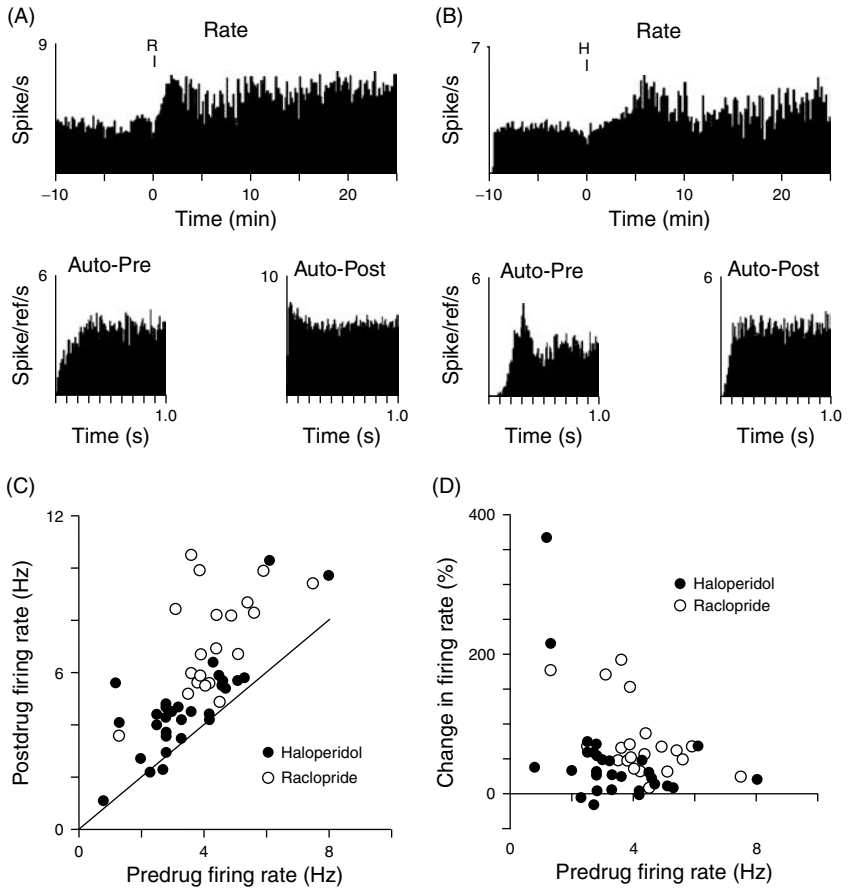

FIGURE 9.1 Effect of D2-receptor blocking drugs on firing rate and firing pattern of dopamine cells recorded in free-moving rats. (A) Rate-meter histogram (top panel; one-second bins) shows increased firing rate in this cell after raclopride injection at time 0 ("R"). The autocorrelogram plots below the histogram, calculated from the 10-min predrug control period (left) and the period 10 to 20-min postdrug (right), show irregular firing before, and enhanced bursting after injection in this cell. (B) A cell showing increased firing rate and decreased regularity of firing after haloperidol ("H"). (C) Relationship between baseline (predrug) firing rate and postdrug firing rate, calculated from period 10 to 20-min postinjection. Diagonal line shows line of equality (no change). (D) Relationship between baseline firing rate and the change in firing rate (difference between pre- and postdrug firing rates expressed as a percentage of baseline rate) induced by D2 antagonists. (Courtesy of B.I. Hyland, personal communication.)

(Gomeza et al., 1999). M4 receptors are colocalized with D1 receptors in many striatal neurons (Ince et al., 1997) implying that their respective effects may be capable of interacting at a subcellular or synaptic level. In rodents (Shannon et al., 2000) and experimental primates (Andersen et al., 2003), behavioral experiments show that agonists at the M4 receptors produce effects predictive of antipsychotic

effects in humans, such as blockade of instrumental conditioning, even though the agonists concerned lack effects on dopamine receptors. It has also been shown that M4 agonists act like dopamine D1 antagonists to reduce the formation of cAMP in striatal cells (Olianas et al., 1996). Acetylcholine, or a nonselective muscarinic agonist, carbachol, has the same effect in membrane preparations from the rat nucleus accumbens or striatum, and this is counteracted by selective antagonists at the M4 receptor (Olianas et al., 1998; Onali and Olianas, 2002). Other work finds similar effects on cell cultures, rather than in the striatum (Zeng et al., 1997). In any case, the behavioral evidence is clear that M4 agonists antagonize the basic psychobiological processes mediating psychosis. The M4 receptor may also have a role modulating that of the M2 receptor, with respect to extrapyramidal motor effects. This is suggested by the finding that, in mice lacking the M4 receptor, catalepsy could still be produced by neuroleptic drugs, but, abnormally, it could not be reduced by the cholinergic antagonist scopolamine (Kanasawa et al., 2003).

With these facts in mind, the idea that D2-blocking neuroleptic drugs act indirectly to produce their antipsychotic effects can still be maintained, with the final target being the D1 receptor or the intracellular mechanisms for cAMP production. However, the details of that indirect action is probably different from that proposed by Miller and collaborators (see this section and Figure 9.2). As in the first hypothesis, it is suggested that D2 blockers lead to increased activity in the striatal cholinergic neurons. However, this then has two independent consequences: via activation of M2 and perhaps other muscarinic receptors, extrapyramidal motor side effects are produced, and via activation of M4 receptors, the reinforcement/incentive function is attenuated, and, in human patients, antipsychotic effects are produced. This new hypothesis is preferable to the original hypothesis of Miller et al. (1990) in that reduction of motor side effects by anticholinergic drugs need not proceed *pari passu* with reductions in therapeutic effects, because the two effects are mediated by different cholinergic receptors. Figure 9.2 depicts the causal relations postulated in the original hypothesis of Miller et al. (1990), together with the revised hypothesis just presented.

The close relation between psychosis and the reinforcement function of dopamine is gaining increased acceptance (Kapur, 2003), but the paradox in this with regard to receptor subtypes involved has rarely been grasped. Reluctance to accept the implication that D1 receptors and cAMP-dependent intracellular mechanisms are primarily involved in antipsychotic action stems largely from the clinical trials, purportedly showing that D1 antagonists have no therapeutic potency. How solid is the evidence on which this conclusion is based? There have been five papers reporting clinical trials of D1 antagonists in psychotic states. A key point in evaluating them is the duration of the trial. This follows from the point made above that the full effect of therapy with antipsychotic drugs takes several (sometimes many) weeks to emerge, the exact time course depending in part on the prior duration of untreated psychosis. According to McDermott et al. (1991), 20% of patients reach a criterion of therapeutic response by day 8 of treatment, 40% between days 8 and 18, and a further 30% between days 18 and 36. Marder (2002) states that "it takes up to 4 weeks on full therapeutic dose to demonstrate convincingly that a patient should be considered a non-responder to that regimen." Some patients require longer treatment than this to reach a criterion of clinical response to neuroleptics (Emsley et al., 2006).

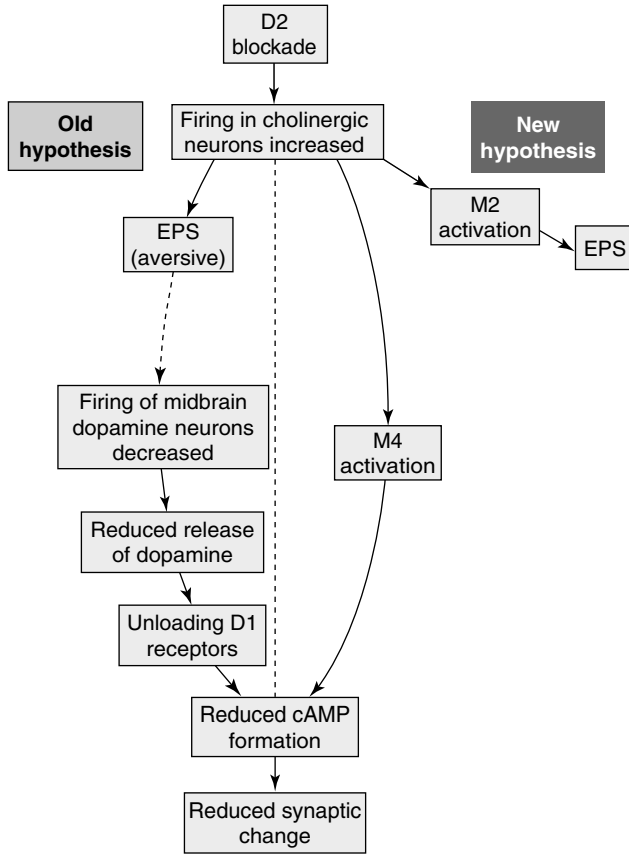

FIGURE 9.2 Alternative hypotheses for indirect action of dopamine D2-receptor blocking antipsychotic drugs. Both hypotheses postulate increased firing of striatal cholinergic interneurons, and that the final common target of antipsychotic drugs is reduced formation of cAMP. *Left*: Indirect action mediated by the aversive effects of extrapyramidal side effects (EPS). *Right*: Indirect action mediated by increased activation of striatal muscarinic M4 receptors.

With these comments in mind, consider the following breakdown of clinical trials of D1 antagonists in psychotic patients: The paper of Gessa et al. (1991) cannot be taken seriously as refutation of a therapeutic effect, because the agent was administered only in single doses. De Beaurepaire et al. (1995) studied six cases. One dropped out after exacerbation of some symptoms by day 14. Two more dropped out after exacerbation by day 21. Of the three who survived the full 28 days of the trial, two showed some improvement. In the study of Den Boer et al. (1995), 12 cases were treated. One patient was lost to follow-up at day 21 with minimal change from baseline. Of the remaining five, who survived 28 days of the trial, two were much improved, one was minimally improved, and two were minimally worse. The mean improvement for the six who survived more than 14 days was greater than that for the

five early dropouts. Karle et al. (1995) studied 11 cases. One case survived 18 days, and was minimally improved, one survived 29 days and was minimally worse, and nine survived 34–39 days. Of the latter one showed no change, four showed minimal improvement, three showed much improvement, and one was very much improved. On the PANSS* positive subscale, 7 out of 11 improved. Karlsson et al. (1995b) studied 17 cases. There was little improvement overall over 4 weeks of the trial, although they did eventually respond well to conventional treatment. Looking at the individual characteristics of the patients, one cannot explain the lack of response in terms of early dropout, differences in duration of illness, or in the duration patients were neuroleptic-free before the trial. However, from baseline clinical ratings it may be that the patients in this study were more severely ill than in the study of Karle et al. (1995), and perhaps that of De Beaurepaire et al. (1995), and therefore would have required longer treatment to show a definite therapeutic effect.

From this summary, and bearing in mind the long and variable time course for therapy with antipsychotic drugs, it is by no means established that D1 antagonists lack therapeutic potency. Given this, and the strong arguments from theory in favor of a role for D1 receptors in psychosis, there is a compelling case for reevaluating the clinical effects of D1 antagonists. A similar recommendation has been made by Peacock et al. (1999).

9.6 POSITIVE FEEDBACK BETWEEN STRIATUM AND CORTEX IN THE GENERATION OF PSYCHOSIS

At the end of Section 9.2, it was suggested that, in generation of endogenous psychoses (such as those of schizophrenia), dyscontrol of midbrain dopamine neurons occurs, as a result of excessive activation via pathways descending from the cerebral cortex. It has also been argued that the basic role of dopamine in psychosis is to produce abnormally potent reinforcement of neural activity in the striatum. Such extremes of activity are relayed to the "motor" thalamus and cortex, with the result that the cortical cell assemblies representing (mainly) cognitive material will also be driven to extreme levels of activation. Such heightened activity will contribute to cortico-striatal activity, whose postsynaptic effects are the target of dopaminergic reinforcement; and it may also raise the excitation of the midbrain dopamine neurons further. In short, a large-scale positive feedback loop may be at work in the generation of psychotic states.

Some indication of this at the whole person level is the fact that endogenous psychotic states often do not arise suddenly but are preceded by a long "prodrome" characterized by increasing psychological abnormality, leading eventually to more rapid acceleration toward full-blown psychosis (Yung and McGorry, 1996). After stabilization with antipsychotic drugs, and the withdrawal of the medication, psychosis does not recur inevitably, but may have an increased probability of recurrence in the next year or two, often in relation to traumatic life events (Steinberg and Durell, 1968; Brown et al., 1973a,b; Jacobs and Myers, 1976; Bebbington et al., 1996).

* Positive and Negative Syndrome Scale (Kay et al., 1987).

These clinical observations are compatible with the view that psychosis arises as a result of entrainment of a positive feedback process at the level of brain dynamics. However, this need not be inevitable: Long periods of relative stability may occur, to be disturbed occasionally by powerful life experiences, at which point the "vicious circle" inherent in the connectivity is set in motion, leading to psychotic destabilization.

Given the potential positive feedback relation (between the striatum, its dopaminergic reinforcement signal, and the neocortex), implicit in the loop of connections just described, and their physiological effects, one is then led to ask the following question: Why do not the structures involved more commonly become entrained in the positive feedback process? In other words, why is endogenous psychosis not more common than it is? These questions become central to the discussion in Chapter 10, where complications of disorders of the basal ganglia are discussed. In answer to these questions, a suggestion is offered for a hypothetical mechanism, which produces relative stability, except under extreme circumstances.

10 Syndromes Arising as Complications of Prolonged Underactivity of Striatal Dopamine Mechanism, and Other Disorders of the Basal Ganglia

10.1 INTRODUCTION

In this chapter, various syndromes are discussed that are best considered not mainly as primary disorders of the basal ganglia, but as complications of some of the disorders already dealt with. Most of them are complications arising from prolonged underactivity of dopaminergic mechanisms in the striatum. This may arise in two ways, either as a result of idiopathic Parkinson's disease, or as a result of prolonged exposure to large doses of dopamine-blocking agents, usually during treatment for psychotic illnesses.

Arguments were presented (Sections 8.2 and 9.5) suggesting that in parkinsonian syndromes, there is overactivity of striatal cholinergic neurons. There is also a widespread increase in the firing rate of striatal medium spiny neurons (Sections 3.4.5 and 8.2), and other consequences follow from this, in the nuclei downstream from the striatum. The exact biophysical reasons for the overactivity of medium spiny neurons are not resolved. It is likely that excessive release of ACh, active at muscarinic M1 receptors, plays a major role in this, although loss of direct action of dopamine on the medium spiny neurons may also make an important contribution (see Section 8.2).

The suggestion has been made (Miller and Chouinard, 1993) that prolonged underactivity of dopamine systems, for whatever reason, leads to a number of distinct syndromes, as a result of the loss of striatal cholinergic neurons. Some of these syndromes are characterized by abnormal movements, but similar pathological processes may lead to symptoms in the cognitive realm, producing psychotic states with the unusual characteristic that they are refractory to treatment with typical antipsychotic drugs. There are three syndromes covered by this hypothesis: (i) *tardive dyskinesia* (TD) (a motor disorder, occurring as a late consequence of prolonged neuroleptic treatment); (ii) the so-called *peak-dose dyskinesia* (PPD), a late complication of Parkinson's disease, revealed during L-DOPA therapy; and (iii) a syndrome first described by

Chouinard et al. (1978), referred to as *neuroleptic-induced supersensitivity psychosis*. The clinical observation that led to the concept of supersensitivity psychosis was that, for some patients with psychotic illness treated with antipsychotic drugs, psychotic symptoms emerge during treatment, or immediately on withdrawal or dose reduction of medication. Withdrawal-emergent psychosis occurs repeatedly each time drug withdrawal is attempted. Such immediate relapse is not typical of the majority of patients with psychotic illness treated with neuroleptics. This led Chouinard and colleagues to identify a separate syndrome, which they called supersensitivity psychosis. To these three syndromes can be added another: (iv) There are some cases of *atypical psychotic illness*, *which*, *regardless of the prior history of neuroleptic treatment*, *are resistant to treatment with conventional antipsychotic drugs*. While these are four separate syndromes, it was suggested by Miller and Chouinard (1993) that they involve similar pathological processes. Therefore, in the subsections that follow, the four syndromes will be taken together, as each strand of evidence is discussed on which the case for a common pathophysiology is based. The main subsections deal with (i) the reasons for identifying striatal cholinergic cell loss as the basic pathology; (ii) details of phenomenology, and their relation to the model of basal ganglionic function developed above; and (iii) examination of the pharmacology of these syndromes. Evidence is not available on all points for all four syndromes. Nevertheless, there is enough evidence to warrant collecting the four syndromes together in this way. Most of the discussion that follows deals with the first three syndromes, each emerging during prolonged dopaminergic underactivity. Whereas Chapters 7 and 8, dealing with Huntington's and Parkinson's diseases, respectively, focused mainly on motor/behavioral symptoms, and Chapter 9 focused mainly on cognitive symptoms of psychosis, the present chapter is able to spell out the parallels between motor/behavioral and cognitive symptoms produced by a similar hypothetical pathology, but supposedly expressed via different functional circuits through the basal ganglia.

The final section of this Chapter (Section 10.6) deals with a number of other syndromes generally thought to involve the basal ganglia, but whose exact pathological basis is at present not well defined.

10.2 REASONS FOR IDENTIFYING STRIATAL CHOLINERGIC CELL LOSS AS THE ORIGIN OF THE FOUR SYNDROMES

10.2.1 Three of These Syndromes Emerge during Prolonged Dopaminergic Underactivity

The first three syndromes mentioned above appear during periods of prolonged dopaminergic underactivity. In the case of TD, the syndrome often appears after some months or years of neuroleptic treatment, the incidence increasing as duration of treatment is increased from a few months up to 10 years (Sweet et al., 1995; van Os et al., 2000). Occasionally, TD appears within a few weeks of the start of treatment (Chouinard and Jones, 1979). TD is not limited to people treated with neuroleptic drugs: It was described in schizophrenia before the neuroleptic era (e.g., by Bleuler [1950, pp. 447–449], who debated whether oro-facial movements had a neuroanatomical or a psychic basis). Nowadays, TD is also sometimes seen in patients

with no previous neuroleptic exposure (Owens et al., 1982; McCreadie et al., 1996). Nevertheless, patients exposed to neuroleptics have a higher incidence of TD than nonexposed patients (Jeste and Wyatt, 1981). These facts suggest that neuroleptic exposure is one amongst a number of possible contributory causes of this syndrome (Crane, 1973a). The relationship of TD to drug exposure is stronger for typical neuroleptic drugs than for the atypical drugs (serotonin-dopamine antagonists and clozapine) (Correll et al., 2004; Margolese et al., 2005). It appears more consistently if neuroleptic drugs produce prominent parkinsonism than in patients with less-severe motor side effects (Kane et al., 1986; Chouinard et al., 1986a, 1988; Tenback et al., 2006). This may be the explanation of the lower risk associated with atypical antipsychotic drugs.

Abnormal dyskinetic movements also occur in some patients with Parkinson's disease during L-DOPA therapy (Barbeau, 1969; Cotzias et al., 1969; Chase et al., 1973) and are commonly referred to as *peak-dose dyskinesia*. This is relatively rare after L-DOPA administration in patients with no preexisting parkinsonian disorder (Barbeau, 1969; Cotzias et al., 1967; Mones et al., 1971; Markham, 1971; Chase et al., 1973), or in normal monkeys (see Section 9.4). Likewise, when L-DOPA was used to treat depression, dyskinesia was rare (Bunney et al., 1969; Goodwin et al., 1970).* There has been debate about whether the occurrence of PDD depends on the duration of treatment with L-DOPA, or alternatively on the duration of the illness itself. However, L-DOPA given long term to nonparkinsonian patients does not lead to the appearance of dyskinesia (Arts et al., 1991). The longer the prior duration of illness, the more severe (Cotzias et al., 1969) or the more common (Mones et al., 1971) are the involuntary movements after L-DOPA. Evidence in unilateral or asymmetrical Parkinson's disease supports these early reports: PDD occurs mainly on the more severely affected side (Mones et al., 1971; Kempster et al., 1989; Horstink et al., 1990). Since both sides receive the same drug treatment, it is likely that severity of illness rather than duration of drug treatment predisposes to PDD. Similarly, the body part showing most severe PDD after L-DOPA corresponds to the part showing most prominent parkinsonian symptoms prior to receiving the drug (Gerlach, 1977). In monkeys, rendered parkinsonian by administration of MPTP, the severity of dyskinesia after giving L-DOPA is usually found to be related to the degree of dopamine cell loss (Schneider, 1989; Boyce et al., 1990b; Alexander et al., 1993). However, this is not always seen (Guigoni et al., 2005), and the relation between dopamine cell loss and the predisposition to dyskinesia after L-DOPA may depend on additional factors.

It has even been reported that early initiation of L-DOPA treatment in human patients with Parkinson's disease may prevent later development of dyskinesia during L-DOPA therapy (Bergman et al., 1987), although Markham and Diamond (1981, 1986) found no evidence for this. This issue is made more complex because there may be more than one effect of regular treatment with L-DOPA. Alleviation over the long term of parkinsonian symptoms may protect against the development of the dyskinetic predisposition; but in those who have such a predisposition, exposure to

* However, as mentioned in Section 9.4, very high IV doses of amphetamine in humans without underlying neurological disease, and sometimes IV or IP doses of L-DOPA in normal monkeys, can lead to the emergence of abnormal movements.

repeated L-DOPA may lead to progressive increase in the severity of the abnormal movements (see Section 10.3). It is difficult to ascertain the first of these effects if the second can also occur. However, the existence of a protective effect is supported by a recent large multicenter Japanese study (Ogawa et al., 1997). Early treatment with the dopamine agonist bromocriptine (which has a low tendency to provoke dyskinesia *de novo*) was associated with minimal appearance of PDD over 10 years. Thus, as with neuroleptic-induced TD, prolonged periods of underactivity of dopamine mechanisms, with manifest untreated parkinsonian symptoms, appear usually to be the necessary condition for appearance of dyskinesia, although high-dose amphetamine or L-DOPA can sometimes produce abnormal movements in neurologically normal humans or monkeys. In some studies (Mouradian et al., 1988, 1989), it is shown that, early in the course of Parkinson's disease, dyskinesias are produced by L-DOPA only at very high doses. As the disease progresses, the dose for alleviation of the Parkinson's disease remains fairly constant, but the higher dose at which dyskinesia is produced progressively falls, so that the dose "window" for effective therapy without dyskinetic side effects becomes progressively narrower.

Supersensitivity psychosis, as mentioned above, is a psychosis, which is atypical in that it occurs actually during treatment with (or soon after withdrawal from) neuroleptic drugs (Chouinard et al., 1978, 1986b; Chouinard and Jones, 1980; Chouinard, 1990). Withdrawal-emergent psychosis was known well before its atypical nature was realized (e.g., by Degkwitz et al., 1970). This pattern of illness is seen in patients with long-term exposure to neuroleptic drugs (Chouinard and Jones, 1980). The time relation between the appearance of supersensitivity psychosis and the history of neuroleptic administration is similar to that for development of TD, and Chouinard and colleagues suggest that they are equivalent pathologies, the latter in the motor domain and the former in the cognitive domain. This is supported by evidence that the expression of the two syndromes often occurs together (Chouinard and Jones, 1980; see also Degkwitz et al., 1970). A recent study (Apud et al., 2003), failed to find a correlation between the presence of TD and exacerbation of positive psychotic symptoms on withdrawal of medication. However, most of the patients in this study were treatment-resistant, and showed substantial positive symptoms even before withdrawal. The patients in whom a correlation between emergence of psychosis and that of dyskinesia on treatment withdrawal can best be demonstrated are those in whom both the psychosis and the TD is masked by medications.

The concept of supersensitivity psychosis is based mainly on longitudinal clinical studies. These case studies differ from typical psychosis, where relapse on drug withdrawal is not automatic, but occurs probabilistically within a year or two (Davis et al., 1989). In such cases, psychotic breakdown is often related to adverse life events in predisposed persons (Jørgensen, 1985; van Os et al., 1994; Bebbington et al., 1996). In the case of supersensitivity psychosis, this typical pattern changes gradually over months and years of treatment, first to an increase of dose requirements, or withdrawal-emergent but transient psychosis, then to withdrawal-emergent psychosis reversed only by reinstating medication, and eventually to psychosis which is resistant to treatment with most antipsychotic drugs (Chouinard and Jones, 1980; Chouinard, 1990). Such atypical psychoses appear not to be related to adverse life events. It may be questioned whether such psychosis is truly neuroleptic-induced, the alternative

being that it is just one of the varied manifestations of a complex endogenous illness. More rigorous proof that it is neuroleptic-induced requires controlled comparisons between patients whose psychotic illness is and is not controlled by neuroleptics. Such a study is difficult to arrange for obvious ethical reasons. It might be achieved by comparing compliant versus noncompliant patient groups with respect to the type of psychosis, or by comparing typical and supersensitivity psychosis with respect to prior history of neuroleptic administration. No such studies have been reported to date. There are, however, occasional case reports where psychosis fitting the criteria for supersensitivity psychosis appears *de novo* after neuroleptic treatment in persons with no preexisting psychotic illness, for instance, when neuroleptics are prescribed for affective disorder (Sale and Kristal, 1978), Tourette syndrome (Silva et al., 1993), or when metoclopramide is prescribed for gastrointestinal disorders (Lu et al., 2002). These cases, though rarely reported, lend weight to the concept of supersensitivity psychosis.

It should also be noted that some Parkinson's disease patients treated with L-DOPA experience psychotic symptoms (Fischer et al., 1990). This appears to be an atypical response to the drug, and may be a manifestation of complications similar to those that lead to TD, PDD, and supersensitivity psychosis. If so, one would expect that psychosis occurring during L-DOPA treatment would be associated with dyskinesia, just as TD and supersensitivity psychosis may be associated, supporting the view that the motor and the cognitive symptoms are equivalent pathologies. This association has been reported by Friedman and Sienkiewicz (1991) in the more severe psychotic reactions reminiscent of endogenous psychotic illness.

10.2.2 These Syndromes Are Persistent, Even Permanent

According to Crane (1973a), drug withdrawal may contribute to recovery from TD, but in a large percentage of cases, symptoms are unchanged, months or years after withdrawal of neuroleptics. The same is usually true for supersensitivity psychosis when well established: Once the pattern of atypical psychosis has emerged, it tends to be persistent (Chouinard and Jones, 1980). Likewise, PDD represents a stage in the advanced progression of Parkinson's disease, which, once established, is persistently expressed whenever L-DOPA is given, a finding also made in MPTP-treated parkinsonian monkeys (Bédard et al., 1986).

10.2.3 Relationship of These Syndromes to Dopamine and Acetylcholine

A key fact about TD is that, despite its appearing as a result of prolonged dopamine blockade, the expression of the syndrome is masked by the acute administration of the same dopamine-blocking drugs (Crane, 1973a). For this reason, the syndrome is often discovered only when medication is withdrawn or dose is reduced (Schultz et al., 1995), although in more severe cases, the dyskinesia can no longer be masked by these drugs. As mentioned above, prominent parkinsonian symptoms predispose to development of TD, but the two motor syndromes rarely coexist (Heinrich et al., 1968; Crane, 1973a). Supersensitivity psychosis shows the same relation to dopamine-blocking drugs, so that this syndrome too is often withdrawal-emergent, is masked by

the medication, and persists despite medication only in severe cases (Chouinard and Jones, 1980; Chouinard, 1990). PDD is provoked by agents that increase dopaminergic tone in patients who otherwise have dopaminergic underactivity. According to Barbeau (1969), when PDD appears, in contrast to parkinsonian rigidity, tendon reflexes are weak and there is hypotonia. When the effect of L-DOPA wears off, and parkinsonian symptoms return, dyskinesia usually stops (but see Section 10.3). Thus, as with the other two syndromes, expression of PDD is masked by prevailing dopaminergic underactivity and presence of parkinsonian symptoms.

TD (like PDD) is exacerbated by administration of dopamine agonists in some, but not all cases (Fann et al., 1973; Gerlach et al., 1974; Casey and Denney, 1977). In the case of supersensitivity psychosis, its appearance may also be related to dopaminergic overactivity, since the preexisting typical psychotic illness may be associated with overproduction of dopamine (see Section 9.2).

In the striatum, it is well known that there is an antagonism between dopaminergic and cholinergic mechanisms (Sections 8.2 and 9.5), seen, for example, in the antiparkinsonian effects of cholinergic antagonists. It is therefore no surprise that expression of TD is increased by cholinergic blockers (Klawans, 1973; Klawans and Rubowitz, 1974; Gerlach et al., 1974; Chouinard et al., 1979; Yassa, 1988). Anticholinesterases, in contrast reduce (mask) the expression of TD, in some but not all cases (Gerlach et al., 1974; Klawans and Rubowitz, 1974; Fann et al., 1974; Tamminga et al., 1977; Caroff et al., 2001). Cholinergic drugs have similar effects on PDD, with antagonists increasing the incidence or inducing ("unmasking") it in Parkinson's disease patients (Birket-Smith, 1974, 1975) and anticholinesterases sometimes abolishing its expression (Lindeboom and Lakke, 1978; Caroff et al., 2006), though this is not always seen (Tarsy et al., 1974). The effect on expression of supersensitivity psychosis produced by cholinergic drugs has not been examined specifically. However, it is known that more typical cases of psychosis are acutely improved by cholinergic agonists or anticholinesterases (Pfeiffer and Jenney, 1957). Betel nuts, widely chewed in tropical regions, contain arecoline as their principal pharmacological agent, this being a nonselective muscarinic agonist. Betel nut chewing is reported to improve psychotic symptoms in persons with schizophrenia (Sullivan et al., 2007). Anticholinergic drugs have also been reported to retard neuroleptic therapy (Singh and Kay, 1973, 1978, 1979; Singh et al., 1987).

10.2.4 Discussion

In early theorizing about TD, it was proposed that proliferation of dopamine receptors was the pathophysiological basis of the syndrome (Tarsy and Baldessarini, 1976; Klawans et al., 1980). The same mechanism was also suggested for PDD (Klawans et al., 1977) and supersensitivity psychosis (Chouinard et al., 1978; Chouinard and Jones, 1980). However, for TD, most empirical studies, comparing matched groups of patients with and without TD have failed to find a proliferation of dopamine D2 receptors. These include three postmortem examinations (Crow et al., 1982; Kornhuber et al., 1989; Reynolds et al., 1992) and three PET studies (Blin et al., 1989; Andersson et al., 1990; Adler et al., 2002). One of the postmortem studies (Reynolds et al., 1992) actually finds a deficit of D2 receptors in TD cases. The only study that has reported

an excess of D2 receptors associated with TD (Silvestri et al., 2000) was a PET study where many patients had been treated with neuroleptics until quite recently (mean of 14 days) before scanning. The excess number of receptors may then have been a transient response to medication rather than a true reflection of the underlying syndrome. Thus, there is little direct evidence for receptor proliferation as the cause of TD. Likewise, in a recent study of parkinsonian monkeys with a dyskinetic predisposition, it has also been shown that there is no excess of D1 receptors compared with nondyskinetic parkinsonian animals (Aubert et al., 2004). However, the fact that each of these three syndromes is a relatively permanent condition suggests a very different pathology, namely, an irreversible loss of some population of neurons.

Since expression of the abnormalities is masked acutely by dopamine blockade or underactivity, despite the fact that such blockade or underactivity, maintained over time, gives rise to the abnormalities in the first place, one has a clue to the nature of the cell loss. These facts suggest that the expression of the syndromes depends on the suppression of activity in a cell type, normally produced by dopamine. Then, dopamine blockade lifts the inhibition, so that activity in this cell type becomes higher, and the symptoms disappear.

As already mentioned (Section 9.5), dopamine normally inhibits neural activity in striatal cholinergic neurons, and cholinergic agonist and antagonist drugs have effects on expression of these syndromes opposite to those (respectively) of dopamine agonists and antagonists. It is therefore attractive to propose that the three syndromes considered here arise from damage to or loss of the striatal cholinergic interneurons. The symptoms would then arise as a result of reduced ACh release. Their masking by dopamine blockers or anticholinesterases (when it occurs) should be due to increase in ACh release from those cholinergic interneurons that remain intact. The fact that, in advanced cases of TD or supersensitivity psychosis, the expression of symptoms is no longer masked by dopamine blockers appears to be an indication that cholinergic cell loss is effectively complete, so that normal function cannot be restored by potentiating the activity of those that remain intact. These varying degrees of pathology probably also explain the fact that dopamine agonists do not always exacerbate TD, and that anticholinesterases do not always improve the symptoms.

Loss of striatal cholinergic cells probably occurs as a result of several contributing influences. Prominent among these is the prolonged excessive activity in these cells accompanying reduction of dopaminergic tone. There are precedents for suggesting that neurons can be damaged or destroyed as a result of prolonged overactivity (Scharfman and Schwartzkroin, 1989), by mechanisms involving excessive intracellular accumulation of calcium ions. There is some pharmacological specificity in the conditions predisposing to TD: D2-blocking neuroleptic drugs are implicated, but chronic administration of D1-selective dopamine antagonists does not lead to appearance or worsening of TD (Lublin et al., 1993; Peacock et al., 1999). This is consistent with the proposed mechanism for cell loss, since dopamine inhibits cholinergic cells in the striatum via actions at D2, not D1 receptors. In addition, prolonged administration of anticholinergic drugs does not lead to TD (Yassa, 1988), although they may exacerbate its expression, once established. This suggests that the pathological process leading to the syndrome is exerted presynaptically, rather than on the postsynaptic side of the cholinergic neurons.

Apart from the general overactivity of cholinergic cells, individual patients may be particularly prone to loss of cholinergic cells, due to constitutional factors independent of dopamine denervation or blockade. In particular, vulnerability to oxidative stress and ineffective mechanisms of inactivating free radicals may play a major role in appearance of TD (Elkashef and Wyatt, 1999). The biochemical mechanisms determining degenerative cell loss and individual vulnerability to it are only partly understood and are quite complex (Lees, 1993). A possible additional effect is that underactivity of dopamine mechanisms can lead to striatal cell loss more generally than in the small fraction of cholinergic interneurons (Mitchell et al., 1994). If this does occur, it makes it more difficult to provide an exact explanation of motor phenomenology of tardive syndromes in terms of underlying cell loss, a topic mentioned in Section 10.3.

10.2.5 Pathology and Neurochemical Pathology in Syndromes Emergent during Prolonged Dopaminergic Underactivity

The evidence presented above, though strong, is indirect. There is a small body of direct evidence indicating loss of striatal cholinergic cells in the syndromes considered here, or in animal models of these syndromes. Older postmortem studies of patients who had TD at the time of death (Gross and Kaltenbäck, 1970; Jellinger, 1977) found pathological changes in striatal neurons indicative of neuronal damage, which were more prominent in brains from patients with TD. Although methods of identifying cholinergic cells were not available at that time, it is noteworthy that neurons of larger-than-average size, now known to be cholinergic interneurons, were mainly affected. Figure 10.1 shows a Nissl-stained section of the striatum, illustrating the marked difference in size between the majority of the neuronal population and the few large cells. A similar loss of large striatal cells has been reported in brains from Parkinson's disease patients (Bugiani et al., 1980). That this loss is of cholinergic cells is supported by a number of postmortem neurochemical studies, which show that in Parkinson's disease there is a loss of the cholinergic marker enzyme, choline acetyl transferase (ChAT; Lloyd et al., 1975; Reisine et al., 1977; Nordberg et al., 1985). The degree of loss varies greatly between patients. One study (McGeer and McGeer, 1971) found no group difference, and another (Rinne et al., 1991) found a small difference, which did not reach significance. None of these studies of Parkinson's disease provide clinical details about possible association of the loss of cholinergic neurons with L-DOPA-induced dyskinesias.

Two recent studies of brains from patients who died with schizophrenia (Holt et al., 1999, 2005) have also documented loss of striatal cholinergic cells. Two earlier studies (Domino et al., 1973; McGeer and McGeer, 1977) found no deficit in ChAT in the striatum from patients dying after a schizophrenic illness, but Heckers et al. (1993) found a reduced number of ChAT-positive cells in the striatum in three out of six brains from schizophrenia patients. The variability between studies and subjects is similar to that for cholinergic markers in Parkinson's disease. No detail is provided in any of these studies about whether the deficit of cholinergic markers was associated with the syndromes of interest here (TD or psychoses nonresponsive to treatment with neuroleptic drugs). However, all patients in the studies of Holt et al.,

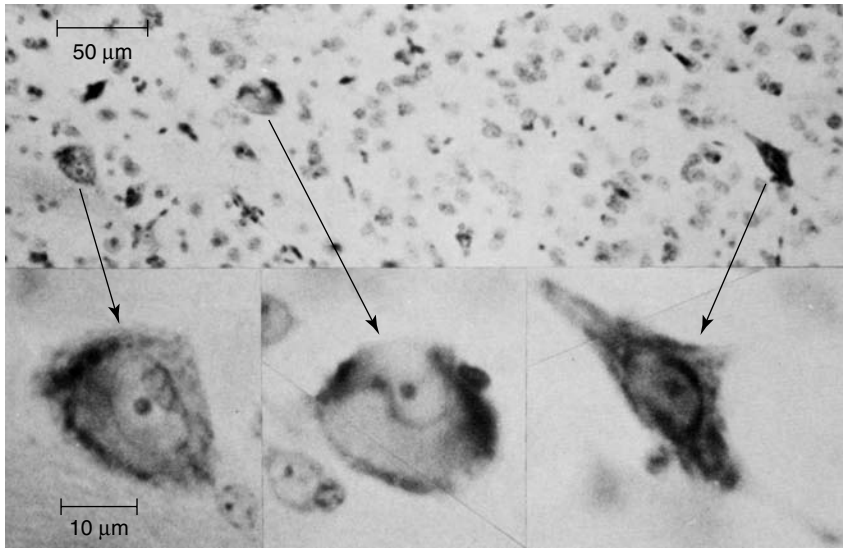

FIGURE 10.1 Kluver-Barrera stain of field of striatal neurons, showing large striatal neurons (which form a small minority of all neurons) as insets. (From Pasik, P., Pasik, T., and DiFiglia, M. in *The Neostriatum*, Pergamon Press, Oxford, 1978. Reproduced with permission from M. DiFiglia.)

had been treated with neuroleptic drugs prior to death, and it is possible that these syndromes were present in some degree. A prediction can be made here: Deficit of cholinergic cells in the striatum should be more severe in schizophrenia patients who suffered TD or supersensitivity psychosis, than in matched patients without these syndromes. Cholinergic cell loss should be more severe in parkinsonian patients showing PDD than in those without this complication.

Animal models of dopamine underactivity provide further support for the proposed mechanism. In rats treated chronically with neuroleptics, it has been reported that there is striatal cell loss, limited to the larger-sized cells (Jeste et al., 1992), and in another study (Mahadik et al., 1988), cells positively identified as cholinergic were shown to undergo pathological changes, including shrinkage and appearance of "shadow cells" after chronic treatment with haloperidol. Such treatment also reduces levels of striatal ChAT (Mahadik and Mukherjee, 1995) in a regionally selective manner (Grimm et al., 2001; Kelley and Roberts, 2004). Chronic treatment of rats with neuroleptics induces abnormal movements in head and face (especially "vacuous chewing"). This condition has been put forward as a rodent model of TD. This has been questioned, since short-term administration of neuroleptics can produce similar abnormal movements. However, the validity as a model of TD of the movements induced by chronic (~6 months) administration of neuroleptics is shown by the fact that the abnormal movements in such rats (though not in those with shorter courses of neuroleptics) is withdrawal-emergent, and masked acutely by reinstatement of neuroleptics (Stoessl et al., 1989; Egan et al., 1996b). Lohr et al.

(2000) demonstrated a correlation between the intensity of such movements, and the loss of striatal cholinergic cells.

Cell loss in the basal ganglia in Parkinson's disease is not limited to cholinergic cells of the striatum. Bernheimer et al. (1973) saw, in postencephalitic and idiopathic PD, in addition to nigral cell loss, pallidal cell loss in about a third of cases (especially in the external segment in idiopathic Parkinson's disease, not correlated with severity of akinesia) and mild cellular atrophy in putamen in over half of 39 cases. Likewise, Bugiani et al. (1980) reported considerable reduction in density of small as well as large striatal cells in Parkinson's disease brain. These facts become relevant in Section 10.3.

10.2.6 Neuronal Dynamics during PDD and TD and the Role of Striatal Cholinergic Interneurons

In Chapter 9, theoretical aspects of dopamine-dependent psychosis were discussed at length. In the present chapter, a parallel has already been drawn between TD and supersensitivity psychosis. If this parallel is valid, we may be able to learn something about neural dynamics in the movement disorders dealt with in this section, from the reasoning used earlier to explain psychosis. In particular, we can identify the abnormal movements of TD and PDD as "psychosis of movement," these being equivalent pathologies, expressed in functional circuits of the basal ganglia other than those involved in psychosis.

In Section 9.5 (see also Figure 9.2), it was suggested that ACh release from striatal cholinergic interneurons leads to the activation of M4 muscarinic receptors on other striatal cells. This, in turn leads to reduction in cAMP formation, itself mediating the synaptic plasticity involved in striatal learning mechanisms. As a result, M4 stimulation has actions similar to those of blockade of D1 dopamine receptors. It follows that, after loss of cholinergic striatal interneurons, the net effect on cAMP formation produced by dopamine is likely to be enhanced, because the inhibition of such formation by tonic ACh release is lost. Therefore, in quantitative terms, stimulation by dopaminergic agents (L-DOPA or natural transmitter release) is likely to have more profound behavioral stimulatory effects after the loss of cholinergic striatal interneurons than when these neurons are intact.

In Section 3.4.4, evidence was reviewed showing that, in parkinsonian models in experimental primates, L-DOPA or apomorphine reduced firing rates in GPi below normal rates, concomitant with reduction of parkinsonian impairments (Filion et al., 1991; Papa et al., 1999; Obeso et al., 2000; Heimer et al., 2002). In cases where L-DOPA produced dyskinesia in these experiments, firing rates in GPi were reduced even more, and firing could be almost completely suppressed (Papa et al., 1999). Correspondingly, in human parkinsonian patients experiencing L-DOPA-induced dyskinesia, cortical activation associated with a simple motor task is substantially larger than normal or in parkinsonian syndromes treated with L-DOPA without appearance of dyskinesia (Rascol et al., 1998). These data fit the idea that PDD occurs during an extreme form of dopaminergic stimulation, more than when L-DOPA alleviates parkinsonism without causing dyskinesia. This conclusion is consistent with effects to be expected when striatal cholinergic cells are lost.

The conclusion is also supported by the study of Rylander (1972) (see Section 9.4), where very high-dose intravenous administration of amphetamine can produce dyskinetic movements in human beings, although this is not generally seen with more moderate doses of this drug. These data support the view that, in quantitative terms at least, PDD is the result of a great excess of cAMP production, the combined result of dopaminergic stimulation and reduced cholinergic tone. Similar statements can be made about TD. They also apply to supersensitivity psychosis, although this involves other functional circuits through the basal ganglia. The relative importance of reduced cholinergic tone (rather than increased dopaminergic stimulation) may be greater in these latter cases.

There is an independent body of evidence, based on investigation of synaptic plasticity and intracellular biochemistry, in support of the idea that, when the dyskinetic propensity has been established, targets of cAMP may be abnormally activated by a mechanism not reliant on activation of D1 receptors. Picconi et al. (2003) studied dopamine-mediated synaptic plasticity in hemiparkinsonian rats. In animals showing L-DOPA-induced dyskinesia, synaptic potentiation induced during high-frequency stimulation was found as in normal rats or hemiparkinsonian rats not showing dyskinesia. However, the dyskinetic rats did not show "depotentiation" (reduction of synaptic efficacy) during low-frequency stimulation. This suggests that some form of stability control has been lost in the dyskinetic rats. These animals also contained abnormally high levels of DARPP-32 ("dopamine and cAMP-regulated phosphoprotein") (as also found in monkeys by Aubert et al., 2004). This substance is necessary for dopamine-mediated synaptic potentiation, dependent as it is on cAMP formation (Calabresi et al., 2000). However, it may also be affected by increase in cAMP resulting from blockade of muscarinic M4 receptors. Notably, in the study of Aubert et al. (2004) in monkeys, it was found that animals with the dyskinetic predisposition had no excess of dopamine D1 receptors. Thus, sensitivity to dopamine D1-mediated stimulation is enhanced without change of the receptors. The relation between DARPP-32 and M4 muscarinic receptors is not clear. However, since M4 blockade leads to increased cAMP formation, the role of DARPP-32 may be enhanced by loss of cholinergic striatal interneurons. It may be that the increase in DARPP-32 in the dyskinetic monkeys is a response to the general increase in intracellular cAMP, consequent on loss of muscarinic M4 stimulation.

It should be noted that PDD is a *qualitative* change from the uncomplicated parkinsonian response to L-DOPA, as well as a quantitative one. In uncomplicated Parkinson's disease, L-DOPA treatment can restore relatively normal movement, without risk of dyskinesia, except at very high doses. According to Mouradian et al. (1988, 1989), as the disease advances, the range of doses (the "therapeutic window") in which parkinsonian symptoms are alleviated without producing dyskinesia progressively narrows, and in severe cases, completely disappears. Thus, as a qualitative change, the progression of the disease leads to gradual contraction of the dose range where relatively normal movement is possible. Instead, the relation between dopamine and movement is either at one extreme (disabling parkinsonism) or the other (disabling dyskinesia). The "region" of stable control is lost. Loss of striatal cholinergic interneurons thus appears to constitute loss of some stabilizing source of control.

In Section 9.6, it was suggested that, in the circuitry involved in generation of dopamine-mediated psychosis, a positive feedback loop might operate between the striatum (and its dopaminergic reinforcement) and neural activity in cortical cell assemblies. When this vicious circle is activated, psychosis progressively intensifies. A similar principle should apply to other functional circuits of the basal ganglia, including those controlling both behavior and movement. When the positive feedback loop is entrained for the functional circuits controlling movement, unintended movements, that is dyskinesia, can emerge. Section 9.6 concluded by asking why psychotic destabilization was not more common than it actually is. We can now suggest an answer to that question: The normal function of the striatal cholinergic cells is to limit the potential for uncontrolled positive feedback, and thus, to widen the range of dopamine activity levels where stable control of movements, behavior, and cognitive function is possible. Specifically, the role of these cholinergic cells is to prevent psychosis and dyskinesia. Recent evidence from experimental animals supports the proposed role of these interneurons in stabilizing basal ganglionic functioning: Kaneko et al. (2000) selectively destroyed cholinergic interneurons in mice by striatal injection of an immunotoxin, and found that the animals then responded to apomorphine with rotation away from the lesioned side, an effect akin to increased dopaminergic tone on that side. Saka et al. (2002) applied to the rat striatum a bacterial toxin, which specifically targets cholinergic and somatostatin-positive interneurons. One week later, when apomorphine was given systemically, the rats also rotated away from the side of the lesion.* In another study, Chiken and Tokuno (2003) used a different toxin with similar selectivity against the large cholinergic interneurons and other GABAergic interneurons, without affecting striatal projection neurons. In subsequent electrophysiological analysis, it was shown that these animals had markedly reduced spontaneous firing rates in neurons of EP, similar to the reduced firing rate in GPi in primate models of dyskinesia.

This stabilizing action can also be inferred from further aspects of the connectivity of the striatal cholinergic cells. Not only do they receive inhibitory input from the dopaminergic innervation of the striatum, but they also receive excitatory inputs from both neocortex and thalamus, notably, from the parafascicular nucleus (Lapper and Bolam, 1992). The importance of these inputs to the cholinergic cells has been studied by Wilson et al. (1990): The rate of tonic firing of the cholinergic cells falls following decortication. After electrical stimulation of cortex or thalamus, it is also reduced in the 100–200 ms poststimulus period, when there is a pause of activity in these regions. The effect of this on striatal dynamics is that, when dopaminergic reinforcement leads to enhancement of cell assembly activity in the cortex, this in turn should lead to increased tonic activity in the cholinergic striatal interneurons, resulting in greater ACh release, greater M4 activation, and reduced cAMP formation. In short, because of the special effects of these interneurons and their excitatory input from cortex and thalamus, a *negative* feedback circuit is introduced to limit

* In the lesioned animals, ipsilateral turning was seen in the first week after the lesion. This was explained, plausibly, by the suggestion that damage to the cholinergic interneurons might change the medium spiny neurons so that they released more SP. As long as the cholinergic neurons were only partially destroyed they would then be stimulated to release more ACh (see Arenas et al. [1991] and Anderson et al. [1993]), mimicking a relatively low-dopaminergic tone on the lesioned side.

the hazards of uncontrolled positive feedback inherent in the basic circuitry of the basal ganglia and their thalamo-cortical targets. Indeed, the effect of ACh release at another muscarinic receptor, the M1 receptor, may also constitute an element of negative feedback. As explained in Section 8.2, when activated, this receptor closes a potassium channel on medium spiny neurons, thus, increasing excitability of these neurons. The converse effect (when increased dopamine activity inhibits the cholinergic interneurons, and reduces ACh release) may be that excitability decreases. Thus, dopamine reinforces cortico-striatal excitatory synaptic efficacy, and, at the same time, apparently to prevent general overactivation, reduces overall neural activity levels in the striatum. Figure 10.2 depicts the essential combined circuitry for these relationships (A), and with the different feedback loops emphasized (positive feedback [B] and negative feedback [C]).

Given these large-scale relationships, and the signs of the various links as defined by known transmitter actions, one can tentatively fill in some of the details of neuronal

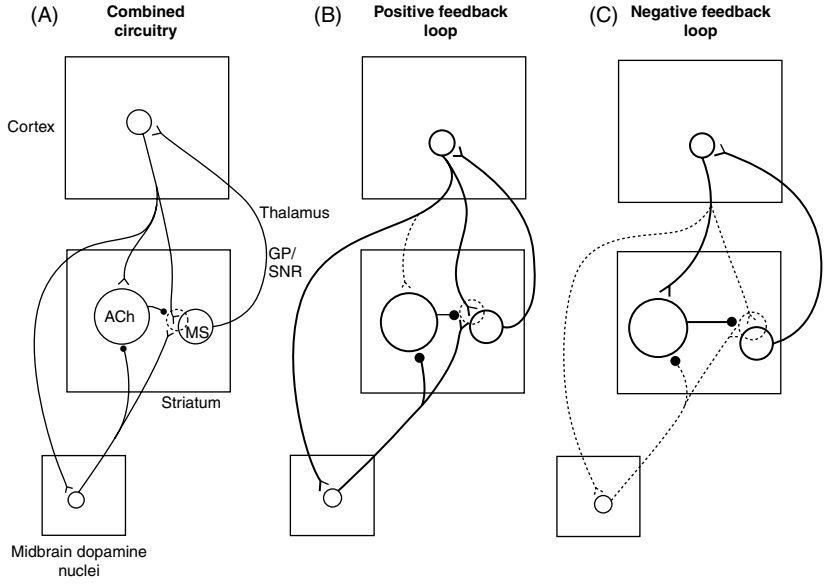

FIGURE 10.2 Feedback loops between striatum and neocortex, and the role of cholinergic interneurons in the striatum. (A) Selected circuitry, combining both positive- and negative feedback components. ACh: Large striatal cholinergic interneurons; MS: Striatal medium spiny projection neuron; GP: Globus pallidus; SNR: Substantia nigra pars reticulata; —≺: Excitatory connection; ——•: Inhibitory connection. (B) The same circuitry, highlighting (bold) connections forming positive feedback loops: (i) from cortex to striatal medium spiny neurons and (via GP/SNR and thalamus) back to the cortex; (ii) from cortex to midbrain dopamine neurons, to potentiation of excitatory synapses on medium spiny neurons and back to the cortex; and (iii) from cortex to dopamine neurons, to inhibition of striatal cholinergic neurons, to suppression of activity and synaptic depotentiation on medium spiny neurons, and back to the cortex. (C) The same circuitry, highlighting (bold) a negative feedback loop, from cortex to striatal cholinergic interneurons, to suppression of activity and synaptic depotentiation on medium spiny neurons, and back to the cortex.

firing rates in the various structures of the basal ganglia, during TD, PDD, and supersensitivity psychosis. Evidence on this is far from complete. Single-unit studies in PDD (or animal models of it) have concentrated on GPi or GPe, but have not examined neurons in the striatum. There is no direct evidence about neural dynamics in supersensitivity psychosis. For more typical psychosis, there is also no direct evidence on neural activity in GP, but studies on striatal neural dynamics in amphetamine-treated rats (mainly the work of Rebec and colleagues, discussed in Section 9.3) is helpful. As in uncomplicated psychosis (for which amphetamine intoxication is our model), one may envisage that in TD and PDD, the reinforcement of cortico-striatal synaptic transmission (dependent on cAMP formation) is excessive. Thus, firing rate of a minority of striatal medium spiny neurons should be enhanced, while that of the surrounding majority should be somewhat decreased. The consequences for GPe, GPi, and SNR would be similar to those after amphetamine. The evidence on this topic is rather confusing (see Section 9.3), probably because one is dealing with mixed effects, change in one direction for some cells, and in the opposite direction for the remainder.

In any case, the net effect is to bring some cells in the motor thalamus (and their connected cortical cell assemblies) to high levels of activity, while firing in many other neurons and assemblies in these structures are relatively suppressed. Evidence that the thalamus is involved in expression of dyskinesia has been obtained in human patients (e.g., Mones et al., 1971; Narabayashi et al., 1980), and has also been documented in MPTP-treated monkeys receiving dopamine agonists (Page, 1992; Page et al., 1993). Thalamotomy has seldom been used as therapy for TD, but in one report of a case with severe antipsychotic-induced tardive dystonia and dyskinesia, thalamotomy reduced the abnormalities (Hillier et al., 1999). Thalamotomy presumably reduces the expression of PDD and TD by reducing the number of activated cells in the thalamus, which can transmit to behavior-related cell assemblies in the cortex. The corresponding unwanted behavior is thus attenuated. It would however be expected that, after thalamotomy, the repertoire of desired behavior would, by the same token, become more limited.

The emergence of dyskinesia is however not simply a product of quantitative reduction in rate of firing in GPi/SNR, but rather of the appearance of abnormal patterns of activity spread over many neurons. This inference helps to resolve one feature about PDD, revealed by neurosurgeons. The "rate hypothesis" of dyskinesia would lead one to expect that lesions or inactivation of GPi should exacerbate dyskinesia, or produce it *de novo*. However, evidence on this is equivocal, and much of it represents a marked contrast to this predicted effect. Several studies have shown that GPi lesions alleviate, rather than exacerbate drug-induced dyskinesia in human Parkinsonian patients (Dogali et al., 1995; Laitinen, 1995; Lozano et al., 1995); the patients then being able to tolerate higher doses of L-DOPA without dyskinesia. Pallidotomy has also been used successfully to alleviate severe TD (Weetman et al., 1997). In animals, dyskinetic syndromes are not seen after GPi inactivation by various means, including local injection of muscimol (Mink and Thach, 1991b; Inase et al., 1996) or kynurenate (Kato and Kimura, 1992), cooling (Trouche et al., 1979), or lesions produced with kainate microinjections (DeLong and Coyle, 1979; Mink and Thach, 1991b). There are however some reports of abnormal movements appearing

after inactivation of GPi. Robertson et al. (1989) reported choreiform limb dyskinesia or hemiballismus after kynurenate injections into GPi. Oro-facial dyskinesia, more typical of TD or PDD was not seen. These authors also produced choreiform dyskinesia by injection of muscimol into the same regions of GPi (Graham et al., 1994). Similar observations were made by Burbaud et al. (1998), choreiform movements being accompanied by an increase in spontaneous locomotor activity.

The beneficial effects on dyskinesia of GPi lesions might be explained by suggesting that, at times when PDD or TD occur, despite the overall low rate of firing of GPi neurons, some GPi cells exhibit changes in firing pattern, in the form of increased burst activity. Evidence for this comes from a report by Matsumura et al. (1995): As mentioned in Section 3.4.3.2, the symptom of chorea in Huntington's disease can be mimicked by microinjection of bicuculline into GPe. When this is done, according to Matsumura et al. (1995), there are changes in firing rates in GPe and GPi, and many neurons in both nuclei develop abnormal patterns of firing consisting of bursts and pauses in association with the dyskinesia. However, this is a model of chorea, not of PDD or TD. Boraud et al. (2000) found, in MPTP monkeys, that L-DOPA produced not only a reduction in firing rate in GPi, but also a *reduction* in incidence of burst firing in GPi, especially for doses that produced PDD. Burst firing was still however more common than in nonparkinsonian monkeys. As discussed in Section 8.6, burst firing is associated more with parkinsonian symptoms than with dyskinesia during treatment for those symptoms. The idea that it is responsible for dyskinesia is not strongly supported.

The only remaining variable that could lead to PDD and TD is the distribution of changes in firing rate across the population of GPi neurons. Three conditions need to be differentiated: the normal state, the hyperkinetic state in Huntington's disease, and the state producing dyskinetic syndromes (PDD and TD) under consideration here. In the normal state, when purposeful active behavior is emitted, the model developed above suggests that a small minority of GPi cells are silenced, while the remainder sustain vigorous tonic activity. As a result, the program for the desired behavior is released, while all other possible activity is suppressed. In hyperkinetic stages of Huntington's disease, owing to indiscriminate loss of cells of origin of the indirect pathway, GPe neurons and GPi/SNR neurons, *in general*, are excessively active and underactive, respectively. There is no overactivity of dopaminergic reinforcement. There is thus a general unselective release of programs for many behaviors, with no indication of their developing progressively as determined by a pathological form of reinforcement. While the resulting activity may retain aspects of motor coordination imposed by lower parts of the motor systems, when considered as goal-directed behavior, it is a confused mixture of many strategies, with no sign of a coherent resultant goal.

In PDD and TD, one might expect, from the foregoing theory, a picture, which, at least in principle, is different from this. In PDD, there is heightened activity of dopaminergic reinforcement supplemented by the effect of cholinergic cell loss. Heightened dopaminergic activity may also be necessary for expression of TD, since it commonly occurs in people who, apart from the movement disorder, are predisposed to psychosis. In these conditions, as in psychotic states (but expressed as movement rather than mainly in cognitive terms), there should therefore be an exaggeration

and distortion of normal functions. As in the studies of Rebec and coworkers using amphetamine in rats, drug-induced enhancement of impulse traffic should occur just in neurons that already show some behavior-related enhancement in drug-free situations. There should not be an indiscriminate fusion of many incompatible strategies. In these syndromes, a larger proportion of GPi/SNR cells are inactivated than in the normal state, and there is overall motor hyperactivity. There may be an excess of unwanted behavior, mixed in with the desired behavior, compared to the normal situation. Some of this may reflect "adventitious reinforcement" (see Section 9.3.1) of neural activity relayed in cortico-striatal pathways, which would not normally become a target for dopamine-mediated synaptic strengthening. Some of it may reflect failure of the striatal collateral inhibition to keep a proper check on overall levels of striatal activity. In general, however, this unwanted release of behavior is not so haphazard and indiscriminate as in the hyperkinetic stages of Huntington's disease. The basic relationship between the neurons in GPi, which are silenced (to signify which behavior to release) and others, which continue firing (to suppress other behavior) is still retained to some extent.

It should be emphasized that the distinction implied here between Huntington's disease and dopaminergic dyskinesias is based on theoretical reasoning. The prediction is that, unlike hyperkinesia in Huntington's disease, many of the abnormal movements of PDD and TD should be exaggerations and distortions of motor programs, or fragments of them, which are within the normal repertoire. Whether this distinction can be made in practice, in observations made in the clinic, is less clear, and is a topic discussed in the next section.

10.3 PHENOMENOLOGY OF PDD AND TD

The term "tardive dyskinesia" covers a wide range of abnormal movements. Early descriptions emphasized that TD typically involves face, mouth, and muscles of mastication. However, Jeste and Wyatt (1982, footnote, p. 51) comment that this early emphasis may have biased many subsequent descriptions. In their own catalog of the phenomenology of TD, abnormal movements could occur in any part of the motor apparatus, including tongue, lips and face, neck and trunk, upper or lower limbs, and even the diaphragm and other parts of the respiratory muscles. Pooling data from several studies, they estimated the weighted mean percentage of TD patients with symptoms in different parts of the body: Oro-facial muscles are affected in 81%. In more detail, the tongue is most commonly and first affected (56% of cases), the lips in 46%, and the muscles of facial expression in 18%. The limbs are affected in 51% of cases (upper limb in 34%; lower limb in 25%), and trunk and axial muscles in 23%. The region affected is a stable characteristic of each patient.

This distribution can be compared with that for PDD. Barbeau (1972) states that L-DOPA-induced dyskinesias usually appear first as facial grimaces or hand stereotypies, spreading to other regions as the dyskinetic predisposition becomes established. Gerlach (1977) reports that TD is more likely to involve the oral region, PDD the neck and extremities. However, increasing age predisposes to oro-facial dyskinesia, younger age to limb dyskinesia, this being the case both for TD (Jeste and Wyatt, 1982, p. 51) and PDD (p. 184). In age-matched groups of patients,

neuroleptic-induced TD is more likely than PDD to involve oro-facial muscles (Jeste and Wyatt, 1982, p. 184).

It is unclear whether abnormal movements in these disorders are of an entirely different nature from those of Huntington's disease. Barbeau (1969) suggested that dyskinesias of PDD differ from those of naturally occurring disorders of the basal ganglia, and resembled those of TD (as far as cephalic manifestations). However, comparing the phenomenology of abnormal movements in the same segment of the body between TD or PDD versus Huntington's disease does not reveal striking differences. Crane (1973b) writes that "when the clinical bucco-lingual-masticatory complex is absent, the problem of diagnosing the disorder (TD) becomes more complicated, because choreiform and other types of motor abnormalities induced by drugs may be similar to those of Huntington's disease." Jeste and Wyatt (1982) also describe the abnormal limb movements in TD as "choreiform." In this context, Goetz and Horn (2004) describe the limb movements of TD as "unpredictable, flowing from one body part to another." However, other descriptions characterize them as stereotyped, that is "reproducible and regular, confined to their anatomic distribution." Likewise, Barbeau (1972) describes PDD movements as having distinct patterns "individualized to each patient" with "a tendency to recur, following the same sequence when Levodopa is again raised after a reduction in dose." This suggests a difference from the apparently random hyperkinetic movements of Huntington's disease.

Since the region of the body involved in these dyskinesias is characteristic of each patient, it is likely that they have a basis in the exact region of the striatum involved in each patient. The fact that body regions affected by the abnormal movements of TD and PDD are characteristic of each patient, whereas, those of Huntington's disease are more widespread, may then be accounted for by the more widespread striatal pathology in the latter condition. The high frequency of occurrence of dyskinesia in the oro-facial regions (especially for TD, but also for PDD) could then arise in several ways: (i) The control mechanisms for movement in the oro-facial region may differ intrinsically from those for other parts of the body, so that the neural machinery for the former is differentially susceptible to dyskinesia. This hypothesis is plausible but lacks detail on the essential difference. (ii) For some reason, cholinergic cell loss may occur more commonly in parts of the striatum controlling oro-facial movements than in other movement-related regions. This is supported by animal work (Grimm et al., 2001) where cholinergic cell loss in rats treated chronically with neuroleptic drugs occurred preferentially in ventrolateral striatum and nucleus accumbens, striatal regions related to oro-facial movement. Kelley and Roberts (2004) also found in rats, which showed vacuous chewing after chronic neuroleptic administration, that the most severe ChAT-positive cell loss occurred in the lateral striatum (actually a region similar to the "ventrolateral striatum" in the study of Grimm et al.). In humans, Holt et al. (2005) found that the number of ChAT-positive cells in schizophrenia was reduced in the ventral striatum but not in the caudate or putamen. The exact topography of the region designated "ventral striatum" is not spelt out, but probably corresponds to the striatal region receiving projections of face representation in sensorimotor cortex. (Flaherty and Graybiel [1993b] illustrate this projection in monkeys, which terminates in ventral putamen.) A detailed explanation

is still lacking as to why there should be such regional differences in susceptibility, but since the preferential involvement of oro-facial regions is determined at least in part by age rather than illness-related factors, in both TD and PDD, it probably applies to both conditions. (iii) One further possible origin to the abnormal movements in TD or PDD is that they arise as a result of "adventitious reinforcement" (see Section 9.3.1), of otherwise unimportant signals relayed from the cortex to the motor parts of the striatum. This is discussed below. If true, it is also possible that the commonness of abnormal movements in the oro-facial region arises because these normally unimportant signals occur more commonly in relays between parts of cortex and striatum dealing with these body regions.

From the reasoning developed in Chapter 9, in relation to dopamine-mediated psychosis, one would expect high-dopamine states to produce elevated firing in a proportion of the striatal neurons of origin of the indirect as well as those of the direct pathway. Therefore, one might expect that, as part of the dyskinetic syndrome produced by L-DOPA, there would be periods of akinesia, with a basis totally different from those occurring in untreated Parkinson's disease. These have been documented, forming the "off" phase of the so-called "on-off" phenomenon during L-DOPA therapy. Barbeau (1972), thus, recognizes two types of akinesia in Parkinson's disease: "normal" akinesia and "akinesia paradoxica," a "positive" effect of L-DOPA therapy in late-stage Parkinson's disease. This is graphically described in *Awakenings* by Oliver Sacks in one of his patients during treatment with L-DOPA:

> She … has almost nothing between coma and hypervigilance, Parkinsonism and frenzy, depression and mania … Both poles indeed may simultaneously occur, and Miss A. will declare, within two or three minutes that she feels wonderful, terrible, can see perfectly, is blind, cannot move, cannot stop moving etc. (With permission from the Wylie Agency. Copyright 1973 by Oliver Sacks.)

Neuropathological examinations of the striatum in advanced Parkinson's disease do also sometimes report significant cell loss in the striatum, beyond the more subtle loss of cholinergic cells, upon which emphasis is placed here (see Section 10.2.5). This might provide an explanation for hyperkinetic movements resembling those of Huntington's disease during PDD or in TD. However, purposeless, apparently random movements could arise as a result of "adventitious reinforcement." In this case, there may be more subtle differences in the basic movement disorder in TD or PDD compared with Huntington's disease, though confounded by pathology additional to cholinergic cell loss. This issue is unresolved and requires detailed study of motor phenomenology. However, in terms of the history of appearance and development of the abnormal movements in each patient, predictions can be made, which should distinguish the movements of TD and PDD from those of Huntington's disease.

If PDD and TD are really equivalents in the sphere of movement disorder to psychosis in the cognitive sphere, the theory of psychosis, developed above, will lead one to expect a number of other specific features in these movement disorders. In Chapter 9, the thesis was developed that psychosis is a distortion and exaggeration of a dopamine-mediated process, similar in some ways to dopaminergic reinforcement of instrumental behavior as studied in animals. There is now good evidence

that, ultimately, these processes are dependent on dopamine-mediated plasticity of excitatory synapses in the striatum. This was part of the explanation offered in Section 9.4 for the protracted time course of therapy for psychosis with antipsychotic drugs. If PDD and TD are produced by equivalent abnormalities of basal ganglionic dynamics in functional circuits concerned with bodily movement, a number of predictions can be made: (i) Dyskinesias occurring during L-DOPA treatment of Parkinson's disease, or on withdrawal of neuroleptic drugs should develop in a manner expected of an exaggeration and distortion of the normal process of dopamine-mediated learning. In other words, specific patterns, once acquired, should persist; and there should be progressive elaboration of the movement disorder, just as systems of psychotic delusions show progressive elaboration during the period of active illness. (ii) These movement disorders should outlast the period of dopaminergic stimulation, just as psychotic symptoms may outlast the period of excessive dopamine activity. In the case of TD, the abnormal withdrawal-emergent movements are masked by reinstating the neuroleptic drugs, but this masking should not necessarily occur immediately. The symptoms should sometimes persist for a period, despite dopamine blockade. (iii) Many of the abnormal movements should be fragments selected from the normal repertoire of purposeful behavior, rather than totally disorganized motor activity, just as much psychotic thought is an exaggeration and distortion of normal thought, retaining some of the meaning and structure of normal thought. (iv) If "adventitious reinforcement" underlies the appearance of some of the abnormal movements, they may be genuinely purposeless and random, although acquired by a variety of conditioning. (v) Since, in terms of neural dynamics (discussed in Section 10.2.6), TD and PDD probably resemble normal dynamics more closely than does hyperkinesia in Huntington's disease, one might expect the subjective side of some of these dyskinesias to be more closely akin to normal voluntary movement.

These fine details of the phenomenology of movement disorders are rarely mentioned in clinical descriptions, and are of little relevance until, with a specific hypothesis in mind, the spotlight falls on them. Therefore, to a large extent, these statements are predictions awaiting evaluation. In particular, the last two of them, pertaining to exact descriptions of movement disorders, may be obscured by pathological processes additional to the essential ones discussed here (see Section 10.2.5 last paragraph). However, there is some evidence in their favor, including the detailed descriptions of L-DOPA-induced dyskinesia, in Oliver Sacks' *Awakenings*. As mentioned above, PDD *does* consist of persisting motor patterns, a formal parallel to persisting delusional themes in psychosis (see prediction [i]). This parallel between motor and psychotic activation is highlighted by the report of Pearce et al. (1995), who mention that the exact form of dyskinesia produced in parkinsonian primates by L-DOPA or dopamine agonists was characteristic of each individual when elicited on repeated occasions. With regard to the gradual elaboration of dyskinesias, the following description is given for one patient during L-DOPA treatment:

> Tics appeared at this time and grew daily.
>
> Within three days of her awakening on L-DOPA, Mrs Y showed the onset of clear-cut tics. These have continually proliferated in number, so much that I can now recognize more than 300 distinct and individual patterns of tic. Every two or three

> days, so to speak, a new tic is "invented"—sometimes seemingly *de novo*, sometimes as an elaboration of an already-existing tic, sometimes as an amalgam or 'conflation' of two or more pre-existing tics, sometimes as a defensive manoevre or counter-tic. (Hester, Y. in *Awakenings*. With permission from the Wylie Agency. Copyright 1973 by Oliver Sacks.)

Similarly, Barbeau (1972) describes how dyskinesias, at first confined to facial regions, then generalize to involve neck and trunk musculature, with abnormal postures maintained for progressively longer periods. Such clinical reports of progressive elaboration of dyskinesias receive support from a recent study of the MPTP animal model of Parkinson's disease. Dyskinesia induced in marmosets by L-DOPA or mixed D1/D2 dopamine agonists grew progressively over 20 or more days of daily administration (Maratos et al., 2003). Likewise, in a mouse model of L-DOPA-induced dyskinesias (Lundblad et al., 2005), doses of L-DOPA, which initially ameliorated the parkinsonian akinesia without producing dyskinesia, developed the capacity to produce dyskinesia when repeated daily for 3 weeks.

For TD, the author is aware of no comparable clinical descriptions. However, in an early German study (Degkwitz et al., 1970) on withdrawal-emergent dyskinesias, tabulated data give the day (after abrupt withdrawal of neuroleptics) on which TD *first* appeared, and when it reached its *greatest intensity*. In men, initial appearance was within 1–5 days (mean of 2 days), and greatest intensity occurs at 1–6 days (mean 3.1 days). In women, withdrawal-emergent dyskinesia appeared between days 1 and 4 (mean 1.8 days) and reached greatest intensity between days 1 and 9 (mean 2.9 days). Jacobsen et al. (1974) also describe two cases of dyskinesia emerging during tailing off (one case) or abrupt cessation (the other case) of haloperidol. In both cases, oral dyskinesias appeared initially, but were subsequently exacerbated by truncal dyskinesia (2 months later; case 1), or arm and leg dyskinesia (2 days later; case 2). These data are not firm proof of time-dependent elaboration of dyskinesias, because they are confounded by the progressive washout of the neuroleptic drug.

With regard to the prediction (ii) (above: the persistence of dyskinesia after the period of excessive dopamine activity), it is noted in several of Oliver Sacks' case reports that quite large doses of L-DOPA are needed for the initial "awakening," but then the dose has to be reduced to much lower levels before the dyskinesias "switch off." In addition, once the dyskinesias have commenced, the times of their onset and cessation often bear little relation to the time of taking the dose of L-DOPA. Barbeau (1972) confirms both these observations. This may be a formal parallel with the persistence of psychotic symptoms long after initiation of adequate neuroleptic therapy. For TD, a recent report of three very severe cases (Walters et al., 1997) describes effective treatment with clozapine (see Section 10.5.2 below). Notably, the improvement occurred slowly over many months, a formal parallel of the slow time course of improvement of long-untreated psychosis, when treatment is eventually possible (see also case 1 of Yovtcheva et al., 2000). Another indication of the persistence of established dyskinesia despite treatment is that, in a long-term follow-up study (The Parkinson Study Group, 2004), patients pretreated regularly with L-DOPA had higher dyskinesia scores when off medication than those pretreated with placebo.

It has been suggested that the predisposition to such dyskinesias is "primed" by the first experience of L-DOPA. Thus, Barbeau (1972) mentioned that the threshold dose for production of dyskinesias falls over the first few months of treatment. Likewise, dopamine agonists (such as the D2 agonist bromocriptine), which do not produce dyskinesias in L-DOPA-naive patients, will do so, if there has been a single experience when L-DOPA produces dyskinesia (Rascol et al., 1999; Damier et al., 2000). Such occurrences are formal parallels of those mentioned in Section 9.4, where psychotic delusions with specific content, once activated, may reappear the next time a patient becomes psychotic.

With regard to prediction (iii), some of Oliver Sacks' descriptions strongly imply that abnormal movements induced by L-DOPA in his patients were fragments of purposeful behavior, rather than uncoordinated motor activity. For instance,

> Her behavior lost what unity it had shown before, and broke into innumerable "sub-behaviors" each perfectly organized and profoundly regressive.
>
> It is clear that Mrs Y's tics are far more complex in form than mere parkinsonian jerks, jactitations or precipitations, and also more complex than the desultory 'quasi-purposeless' choreic and hyperkinetic movements seen in most patients with ordinary Parkinson's disease, with long administration of L-DOPA. Mrs Y's tics *look* like actions or deeds—and not mere jerks or spasms or movements. One sees, for example, gasps, pants, sniffs, finger-snapping, throat-clearing, pinching movements, scratching movements, whose abnormality lies in their incessant compulsive and inappropriate repetition. (With permission from the Wylie Agency. Copyright 1973 by Oliver Sacks.)

It should be emphasized that this quotation refers to the phenomenon of "ticcing," which is not typical of all L-DOPA-induced dyskinesias. If more typical abnormal movements of TD or PDD were to be brought within the same perspective, it would be necessary to show that they (or at least some of them) were related to limb or facial gestures, which had been part of the patient's repertoire of movement before the appearance of recognizable dyskinesia. It is unlikely that this accounts for the full range of abnormal movements in TD or PDD, but it may account for some. Others may reflect "adventitious reinforcement" of otherwise unimportant signals reaching the striatum, giving rise to abnormal movements, which, in no sense, are fragments of once-purposeful behavior. This would correspond to prediction (iv) above.

With regard to the prediction (v, on the subjective experiences accompanying TD or PDD), various accounts suggest that the abnormal movements (especially tics) are partly under voluntary control. Patients may experience a growing urge to perform the movements, which can be resisted in the short term, although the abnormal movement eventually bursts forth regardless. The definition given by Goetz and Horn (2004) of the specific symptom of "tardive akathisia" is relevant here: "an unpleasant sensation of internal restlessness that is partially relieved by volitional movements, occurring in patients who have received chronic neuroleptics." For postencephalitic parkinsonism with PDD, one of Sacks' patients (Leonard L.), finds that the succession of abnormal tic movements could be eliminated by concentrating on other activity (nonstop writing). The exact manifestation was often tied to the overall context, and influenced by psychosocial factors in the outside world. The movements of TD

may also be reduced temporarily by voluntary effort, and by voluntary movements of affected parts (Jeste and Wyatt, 1982, p. 55). This may reflect the local spread of inhibition within each field of the striatum (discussed in Part I, and referred to as "activity control"). In contrast, dyskinetic movements are increased by voluntary movements of other, unaffected parts (Jeste and Wyatt, 1982, p. 55) as they are by increased stress and emotion. This, presumably, is a reflection of more generalized increases in neural activity afferent to the striatum.

10.4 DYSKINESIAS, STEREOTYPY, REFRACTORY PSYCHOSIS AND OTHER BEHAVIORAL PATHOLOGIES RELATED TO HIGH-DOPAMINE STATES WITHOUT A PRIOR HISTORY OF PROLONGED DOPAMINERGIC UNDERACTIVITY

It is known that high-dose amphetamine can induce dyskinesias and stereotyped behavior in humans (Section 9.4). While these may occur in undrugged subjects with evidence of brain damage, they are not limited to such subjects (Jeste and Wyatt, 1982). Stereotypies are very plausibly viewed as abnormally reinforced fragments of behavior within the normal repertoire. For dyskinetic movements, it is more difficult to tell the extent to which they are fragments of purposeful movement programs, as opposed to truly uncoordinated movements. However, Mattson and Calverley (1968) describe them as tic-like, and in one case could be controlled with voluntary effort.

Given the occurrence of dyskinesias and stereotyped behavior in high-dopamine states, without a history of Parkinson's disease or extensive treatment with dopamine-blocking drugs, it is expected that similar phenomena might also occur spontaneously in naturally occurring psychotic states, in patients with no experience of neuroleptic drugs. Stereotyped movements and spontaneous dyskinesias were known to both Kraepelin and Bleuler, although these two interpreted the movements in very different ways. More recently, spontaneous dyskinesias and stereotypies have received less attention, since they are obscured by acute extrapyramidal side effects of neuroleptic drugs, or are complicated by the presence of TD. Nevertheless, they are well documented (Rogers, 1985), although their prevalence varies widely between studies (Bocti et al., 2003). Like TD, such spontaneous dyskinesias tend to occur most commonly in oro-facial regions (Owens et al., 1982; Fenton et al., 1994; Chaterjee et al., 1995; McCreadie et al., 1996; Gervin et al., 1998; Puri et al., 1999), although they do occur in other body regions, and in one study favored the limbs (Fenn et al., 1996). It is not clear whether they are phenomena similar to TD and PDD. In particular, it is not clear whether, like TD, these dyskinesias can be masked acutely by neuroleptics. Moreover, the relationship between such dyskinesias and concurrent psychosis is not well documented. There are several comparisons of prevalence of dyskinesias between neuroleptic-naive and neuroleptic-exposed patients, but none reveal the acute effects of medication. However, Puri et al. (1999) found similar rates of dyskinesia in a comparison of untreated first-episode schizophrenia patients and others who had been treated for a mean duration of only 22.8 days. This suggests that spontaneous dyskinesias in psychotic patients are not usually masked by neuroleptics.

In Section 10.2.1, it was mentioned that L-DOPA can induce dyskinesia in early Parkinson's disease, if the dose is high enough, although the dose window for dyskinesia-free treatment contracts as the disease progresses (Mouradian et al., 1988, 1989). This suggests the following line of reasoning for amphetamine-induced dyskinesias: It has already been proposed that TD or L-DOPA-induced dyskinesia arising after prolonged DA underactivity is due to striatal cholinergic cell loss. Dopamine normally suppresses activity in such cholinergic cells. Therefore, if dopaminergic tone is high enough (as after administration of large doses of amphetamine or kindred drugs), these cells can be silenced completely, thus, mimicking temporarily, the state of actual cholinergic cell loss. In this situation, the same dyskinetic symptoms may occur without a history of prolonged dopamine underactivity.

For spontaneously occurring dyskinesias in neuroleptic-naive patients with psychotic illness, dopamine overactivity may also play a role, but there is an additional possibility. The striatal cholinergic interneurons, rather than having been lost as a result of prolonged Parkinson's disease or neuroleptic treatment, might be reduced in number *ab initio*. In Section 9.5, it was argued that the normal therapeutic responsiveness of psychotic states to antipsychotic drugs depends on increased release of ACh from these neurons, and therefore on the integrity of such neurons. In Section 10.2.4, it was also suggested that complete loss of such neurons may lead to psychoses, which cannot be masked by typical antipsychotic drugs, leading to drug-refractory psychoses. Following these lines of reasoning, one would predict that psychoses occurring in patients who, *ab initio*, have a deficit in the number of striatal cholinergic interneurons, would also be treatment-refractory. There is currently no evidence to evaluate this prediction. However, it is well recognized that psychoses are sometimes refractory to treatment with a variety of antipsychotic drugs. While this condition, like TD, may sometimes be neuroleptic-induced, it is also possible that it occurs for other reasons. One might also expect that psychotic patients showing dyskinesias even before neuroleptic treatment might be more resistant to treatment than those without such dyskinesia. However, this is a less-clear prediction, since spontaneous dyskinesia and refractory psychosis would be expected to depend on lack of cholinergic cells in different striatal regions, which need not occur in close correlation. Again, there is no evidence on the prediction.

The last point in this section is somewhat speculative. The arguments presented in this chapter suggest that the various dyskinetic and psychotic complications of disorders of the basal ganglia are due to pathological manifestations of dopaminergic reinforcement. Such reinforcement is also important in many forms of addiction. These addictions involve especially, the dopamine influence on the limbic striatum (Di Chiara et al., 2004). This may be an indication that addictive behavior is a pathology of basic motivational selection, rather than selection of particular responses or behaviors, and with the potential to dominate the motivational structure of an entire personality. There are diverse determinants of addiction, including many in the realm of the social environment. However, it is also well documented that these determinants include constitutional (including genetic) factors (Crabbe, 2002). One may ask about the basis of these constitutional factors in brain biology. In view of the model presented in this chapter, a possible basis is a relative lack of cholinergic interneurons in critical parts of the striatal complex.

10.5 PHARMACOLOGICAL THEORY: INVOLVEMENT OF DOPAMINERGIC AND CHOLINERGIC RECEPTOR SUBTYPES

In Section 9.5 (see also Figure 9.2), it was proposed that therapy for psychosis with D2-blocking drugs is an indirect effect. It was suggested that it depends first on activation of cholinergic neurons, which leads to increased ACh release, and then activation of M4 muscarinic receptors on other striatal cells. This in turn leads to reduction in cAMP formation, itself mediating the abnormal synaptic plasticity supposed to be involved in active phases of psychosis. As part of the same hypothesis, it was suggested that D1-blocking drugs, which act synergistically with M4 muscarinic blockade, might also have antipsychotic properties. A critique was offered of clinical trials with such drugs, purporting to show that they have no such effect. These suggestions are a rather radical departure from currently accepted views. However, if they are correct, and if PDD and TD *are* motor equivalents of dopamine-mediated psychosis, other propositions follow in the domain of dyskinesia: (i) PDD and TD should be provoked by D1 agonists and alleviated with D1 antagonists. D2 agonists and antagonists should have less (or no) effect. (ii) PDD and TD should be provoked by M4 antagonists and alleviated by M4 agonists. A summary of the pharmacological relations of these syndromes is depicted in Figure 10.3.

10.5.1 Agonists and Antagonists Selective for D1 versus D2 Dopamine Receptors

The evidence with receptor-selective dopaminergic drugs, in favor of the above predictions includes the following results: Peacock et al. (1990; see also Lublin et al., 1993) found that the D1 agonist SKF 81927, but not the D2 agonist quinpirole

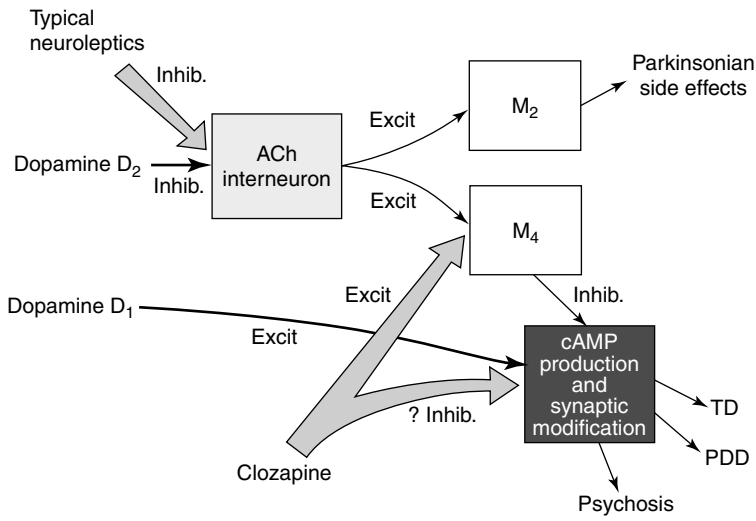

FIGURE 10.3 Proposed pharmacological determinants of TD, PDD, and supersensitivity psychosis.

exacerbated dyskinesia in monkeys already mildly dyskinetic as a result of chronic regimes of haloperidol. Likewise, the D1 agonist SKF 82958 induced dyskinesia in Parkinson's disease patients, although it relieved the parkinsonism (Blanchet et al., 1996). Boyce et al. (1990a) showed that during its short period of action the D1 antagonist SCH23390 abolished dyskinesia, but not the antiparkinsonian effect of L-DOPA. Abnormal movements in rats are attenuated by reduction of dopamine D1 receptor numbers with antisense oligonucleotides to such receptors (van Kampen and Stoessl, 2000).

Studies on human patients with Parkinson's disease (Rascol et al., 1979; Lees and Stern, 1981) as well as MPTP parkinsonian monkeys (Bédard et al., 1986) found that bromocriptine (a D2-selective agonist) given as the only treatment failed to provoke dyskinesia. Likewise, another D2-selective agonist, ropinirole, has a low tendency to induce dyskinesia in MPTP parkinsonian marmosets, unless their dyskinetic tendency has already been primed by L-DOPA treatment (Pearce et al., 1998; Fukuzaki et al., 2000; Maratos et al., 2001).

Several studies support the predictions by showing that agents such as L-DOPA or apomorphine, which lead to increased activation of both D1 and D2 receptors, provoke dyskinesia, while drugs acting solely on the D2 family of receptors were less effective in this regard. These include a study in MPTP-treated marmosets, comparing the effects of L-DOPA with those of piribedil (a D2/D3 agonist) (Smith et al., 2002), a similar study in a mouse model of PDD (Lundblad et al., 2005), and a study on 6-HD-treated rats comparing chronic treatment with apomorphine (a mixed agonist) with quinpirole (a D2 agonist) (Delfino et al., 2004). In humans with Parkinson's disease, treatment with lisuride (a D2 agonist) led to dyskinesia less commonly than treatment with L-DOPA (Rinne, 1989). Likewise, treatment with ropinirole led to the emergence of dyskinesia in only 8% of patients, compared to 23% of those treated with L-DOPA (Rascol et al., 2000), and this development occurred later than during L-DOPA treatment (means of 214 versus 104 weeks). L-DOPA did not differ from a fully selective D1 agonist in its capacity to produce dyskinesia (Rascol et al., 2001).

In apparent contradiction to the predictions, Pearce et al. (1995) found that either D1- or D2-selective agonists could reproduce the dyskinetic symptoms in parkinsonian monkeys produced by L-DOPA. Gomez-Mancilla and Bédard (1991) also found that D2 agonists could reproduce dyskinesia, previously established in parkinsonian monkeys using L-DOPA. Grondin et al. (1999) and Taylor et al. (2005) showed that selective blockade of either D1 or D2 receptors could alleviate L-DOPA-induced dyskinesias. These authors conclude that either dopamine receptor subtype can mediate dopaminergic dyskinesias. However, the force of this conclusion is lessened, by noting that the animals in all these studies had been "primed" to produce dyskinesia by prior L-DOPA treatment (which was also used to maintain their general health after induction of parkinsonism). As mentioned in Section 10.3, such priming may lead to dyskinesias in response to D2 agonists, which are not produced in L-DOPA-naive animals. In the studies of bromocriptine mentioned above, where no dyskinesias were produced, the drug was indeed given to L-DOPA-naive animals.

Results with other D2 agonists cannot be explained away in this manner: The highly selective D2 agonist (+)PHNO provokes dyskinesia in MPTP parkinsonian

monkeys, after several days of administration, when there has been no priming by prior treatment with L-DOPA (Gomez-Mancilla and Bédard, 1992; Luquin et al., 1992). Goulet and Madras (2000) obtained similar results with both (+)PHNO and another selective D2 agonist (quinelorane), the dyskinesias being more pronounced than those produced by the D1 agonist SKF 81927. Animals in the latter study were not primed with L-DOPA, although they had received quinelorane, to minimize overall disability and maintain feeding. These discrepant results might be explained by suggesting that some remaining dopaminergic tone is available to activate D1 receptors, and this collaborates with D2 stimulation, just as occurs with L-DOPA. This is supported by the finding in the study of Gomez-Mancilla and Bédard (1992) that (+)PHNO-induced dyskinesia could be prevented if dopamine synthesis was also blocked; and it could then be reestablished by addition of a subthreshold dose of a D1 agonist. That this cooperative effect is not seen with bromocriptine can be accounted for by the fact that this drug has some D1-antagonist potential (Trabucchi et al., 1976; Markstein et al., 1978). The results of Luquin et al. (1992) cannot however be explained in terms of D1/D2 cooperation, since (+)PHNO administration led to dyskinesia even when preceded by a dose of a D1 antagonist. The argument might also be thought hard to sustain in view of the low level of surviving dopamine innervation in human Parkinson's disease, or MPTP-induced equivalents. However, it is also likely that D1 receptors will have proliferated in such conditions, thus sensitizing striatal neurons to D1 stimulation. Overall, the evidence on receptor-selective dopaminergic drugs in relation to dyskinesia is somewhat equivocal, but is mainly consistent with the predictions made above.

10.5.2 Muscarinic Receptor Subtypes and the Special Efficacy of Clozapine, and Other Agents

The prediction made above about muscarinic M4 agonists and antagonists in relation to dopaminergic dyskinesias cannot be readily addressed from currently available evidence. The identification of muscarinic receptor subtypes is more recent than that of dopaminergic receptor subtypes, and there is a very limited range of agonists and antagonists available with any degree of specificity for the M4 subtype. However, this receptor subtype becomes relevant to another difficult pharmacological question, the unusual and fortunate properties of the drug clozapine. Before discussing its relation to muscarinic receptor subtypes, background information about this drug must be reviewed.

Clozapine is unusual among antipsychotic drugs in several respects. (i) It has a very low tendency to produce acute extrapyramidal symptoms, both in humans (Casey, 1989) and animals (Miller, 1987). (ii) It is effective as an antipsychotic agent but with lower occupancy of dopamine D2 receptors than almost all other dopamine-blocking antipsychotic drugs (Farde et al., 1992; Nyberg et al., 1999). (The other exception is quetiapine, discussed below.) (iii) It is effective treatment in a proportion (~30% of cases) of psychoses, which are otherwise refractory to treatment with antipsychotic medicines (Kane et al., 1988). (iv) It has a low propensity to produce new cases of TD (Kane et al., 1993; Peacock et al., 1996; Margolese et al., 2005). (v) Clozapine is generally thought to alleviate the expression of established TD

(Lieberman et al., 1991). To prove this conclusively, severe cases of TD need to be studied, since antipsychotic drugs generally mask the milder symptoms, while promoting development of the underlying predisposition. However, in severe TD, when this mask is no longer effective with typical drugs, clozapine still reduces TD (Walters et al., 1997; Dalack et al., 1998; Bassitt and Neto., 1998), and the alleviation of symptoms has also been shown in a long-term follow-up study (e.g., Peacock et al., 1996). However, Modestin et al. (2000) found that long-term extensive use of clozapine did not reduce the incidence of TD in their group of patients. Thus, some patients continue to express TD despite long-term clozapine treatment. (vi) Clozapine is also able to alleviate L-DOPA-induced PDD in humans with Parkinson's disease (Bennett et al., 1994; Durif et al., 1997) or MPTP-lesioned monkeys (Grondin et al., 1999).

It has also been reported in several studies that clozapine withdrawal in formerly dyskinetic patients leads to reemergence of severe TD (Simpson et al., 1978; Ahmed et al., 1998; Yovtcheva et al., 2000), which may be worse than the initial dyskinetic state. This might be considered to be an unmasking of TD, similar to that occurring when typical neuroleptic drugs are withdrawn. However, given the evidence that TD rarely emerges during continued clozapine treatment, as it can with continued treatment with typical neuroleptics, this reemergence is probably a different phenomenon, perhaps related to some form of genuine receptor supersensitivity. In any event, although clozapine reduces the expression of TD, it does not cure the predisposition.

Clozapine has a very complex pharmacology, which has permitted a number of proposals to be made to account for its special properties. It is a serotonin–dopamine antagonist, like other more recently introduced atypical drugs (risperidone, olanzapine, etc.). However, it appears to be different from them in its low D2 occupancy in therapeutic doses (Farde et al., 1992; Nordström et al., 1995; Nyberg et al., 1999) and its proven efficacy in refractory cases of psychosis (although the efficacy of the new atypical drugs in this respect is not yet fully evaluated [see Chakos et al., 2001]). Thus, its affinity for serotonin receptors is unlikely to explain its unique effects. Clozapine is also an antagonist at dopamine D4 receptors (Van Tol et al., 1991), which suggested that this underlies its special properties. However, clinical trials of a selective D4 antagonist, including two large studies with relatively low-dropout rates over 4–6 weeks of the trial failed to find any improvement in symptom rating compared to placebo-treated patients (Kramer et al., 1997; Truffinet et al., 1999; Corrigan et al., 2004). Blockade of D4 receptors thus does not appear to have any antipsychotic effect, let alone an effect in refractory cases of psychosis. A third suggestion, based around the role of D2 receptors, is that atypical antipsychotic drugs dissociate from the D2 receptor faster than typical ones, so that the drug can be temporarily displaced by surges of the transmitter dopamine (Kapur and Seeman, 2000). As a result, it is proposed, prolonged occupancy of the D2 receptor by the blocking agent, supposed to underlie the acute extrapyramidal side effects, is avoided. The empirical data on which this hypothesis is based are that the dissociation rate for clozapine is fast. However, other atypical drugs such as sertindole and olanzapine are well within the range of typical drugs in the rate of dissociation, so this hypothesis cannot explain atypicality in general. Furthermore, while the argument of Kapur and Seeman (2000) is used to explain lack of acute extrapyramidal side effects, it is not clear how it explains other atypical features of clozapine.

All the above attempts to account for the unique properties of clozapine are based on receptor pharmacology and its correlation with observed clinical differences between clozapine and other antipsychotic drugs. However, correlations may arise for many reasons, and are not the same as explanations. None of these hypotheses attempts to incorporate the strong body of psychobiological theory, presented in previous chapters, purporting to provide true causal explanations of psychotic and dyskinetic phenomenology in terms of the actions of dopamine in the striatum. If we do take that theory seriously, the spotlight falls on two receptor subtypes dismissed in the above accounts, namely, the dopamine D1 receptor and the muscarinic M4 receptor, which appears to have a role in opposition to the D1 receptor. Can the special properties of clozapine be explained in terms of actions at either of these receptors?

There is evidence for the involvement of both these receptor subtypes in the actions of clozapine. Since D1 stimulation and M4 blockade have, as a common effect, the enhancement of cAMP formation leading to behavioral changes, much of the evidence is compatible with involvement of either receptor subtype, without specifying which. For instance, in a review of the behavioral effects in animals of clozapine, it was concluded that this drug has much closer similarities to those of standard D1 antagonists than to those of D2 antagonists (Josselyn et al., 1997), a conclusion compatible with clozapine acting either as a D1 antagonist or an M4 agonist. However, some evidence points more specifically to a role for D1 blockade in clozapine's actions. Clozapine does have D1-receptor binding properties, its affinity for these receptors being somewhat higher than for D2 receptors (Andersen et al., 1985, 1986; Hyttel and Christensen, 1983; Hyttel et al., 1989). Another indication that clozapine might owe its actions to blockade of D1 rather than D2 receptors is a number of studies in animals showing that clozapine administration leads to proliferation of D1, but not D2 receptors (Seeger et al., 1982; Rupniak et al., 1985; O'Dell et al., 1990; Lang et al., 1992). Admittedly, some caution is needed in applying animal results to humans. In addition, the drug flupenthixol has affinity for D1 receptors equal to or higher than that for D2 receptors (Andersen et al., 1985), but in clinical terms is a typical neuroleptic (Wistedt and Ranta, 1983; Ehmann et al., 1987). Moreover, in a membrane preparation from rat striatum, clozapine failed to inhibit the enhanced formation of cAMP stimulated by a D1 agonist (Olianas et al., 1997).

A small number of recent papers report that clozapine is effective at M4 receptors, although, since there are no selective radioligands for this receptor, the evidence is limited. Bolden et al. (1992) and Bymaster et al. (2003) showed that clozapine bound with high affinity to human-cloned M4 receptors expressed in Chinese hamster ovary (CHO), and Michal et al. (1999) found it to displace muscarinic ligands from the M4 receptor expressed in such cells. Zorn et al. (1994) found clozapine to be a full M4 agonist in the same preparation as assessed by its inhibition of cAMP stimulation (by the agent forskolin). Michal et al. (1999) also found that clozapine inhibited cAMP formation in CHO cells expressing the M4 receptor, although Olianas et al. (1997) found it to have both agonist and antagonist properties under different conditions. However, in rat striatal tissue, Olianas et al. (1997) found clozapine to antagonize rather than mimic the effect of ACh in suppressing cAMP formation. Zeng et al. (1997) found it to have neither effect. In a review of this subject, Bymaster et al. (2003) express caution about an M4 agonist role for clozapine.

Advance in this field will be greatly aided if specific agonists and antagonists for the M4 receptor can be found. Part of the puzzle of clozapine is that it is known often to cause hypersalivation. This has been attributed to an agonist role at peripheral M4 receptors, although this is not clearly established (Davydov and Botts, 2000).

Clozapine is not the only agent of interest in therapy of refractory psychosis, TD, or PDD. Quetiapine (Seroquel) has been reported to be effective in a few single-case studies of severe refractory schizophrenia (Szigethi et al., 1998; Brooks, 2001) and in a 4-week clinical trial of 12 refractory patients (Sacchetti et al., 2004). Moreover, it has been reported to attenuate L-DOPA-induced dyskinesias in primates (Oh et al., 2002). Like clozapine, it has a low D2 occupancy when used in therapeutic doses (Küfferle et al., 1997; Gefvert et al., 2001; Tauscher et al., 2004). Unlike clozapine, it has a relatively low affinity for D1 compared to D2 receptor (Schotte et al., 1996). It has a low affinity for all of the five muscarinic receptor subtypes (Bymaster et al., 2003). However, since it is a low-potency drug overall, its affinity for the M4 receptor compared to the D2 receptor could give the former some role in its therapeutic effects. Nevertheless, there are other hypotheses to account for its atypical properties: It is the only drug with a rate of dissociation comparable with clozapine (in fact faster than it) (Kapur and Seeman, 2000; Kapur et al., 2000).

Another agent meriting brief mention here is ceruletide, an analog of the peptide transmitter and gastrointestinal hormone cholecystokinin. Several studies have claimed this to have antipsychotic properties (Moroji et al., 1982; Verhoeven et al., 1986) although this has not been widely replicated, nor has it been shown to apply to refractory psychosis. The reason for mentioning it, however, is that two studies have shown this agent to alleviate TD in humans (Nishikawa et al., 1985; Kojima et al., 1992). Ashizawa et al. (1996) investigated its action in the rat model of TD (produced by several months of treatment with neuroleptics). After such treatment, dopamine-stimulated adenyl cyclase activity was increased. Ceruletide reduced both the abnormal movements and the activity of this adenyl cyclase. Whether or not the D1 or M4 receptor is involved in the action of ceruletide, it is pertinent that the motor abnormalities are linked to striatal adenyl cyclase activity. There may be ways of modifying the activity of this enzyme, of relevance to human therapy, which involve mechanisms other than those (via D1 or M4 receptors) considered here.

10.6 OTHER DISORDERS INVOLVING THE BASAL GANGLIA

The disorders which have been the focus in Part II of this book are those whose primary pathological basis is known or strongly suspected as having a location in the basal ganglia (usually in the striatum). For these disorders, basic pathology (or neurochemical pathology) correlates well with their various symptom profiles. Hence, these disorders can be defined as distinct entities. They can then be the subject of theoretical analysis, to establish why, in terms of causal reasoning, the symptoms take the form that they do. The chief emphasis of the second part of this book has been to develop such reasoning, and thus to formulate cross-level explanations of symptom profiles in terms of neuronal dynamics.

For a number of other disorders, there is evidence that structures of the basal ganglia are somehow involved in expression of symptoms, but without clear evidence

that the essential pathology is centered in these structures. Generally, these disorders are in the frontier zone between neurology and psychiatry. Without the convergence of evidence about essential pathology and symptoms, these disorders have less-distinct definition than those considered so far. The symptoms involved are in the realms of selection of motor programs and behavior, and in attentional selection. The theory of the normal basal ganglia developed in Part I of this work grouped such functions together under the heading of "executive functions." It is, therefore, plausible that these less well-defined conditions *are* disorders of the basal ganglia. However, without clear evidence that the root causes lie within these nuclei, it is not possible to develop exact causal reasoning, to explain their manifestations in terms of neural dynamics. In the remaining subsections of this chapter, four such disorders will be discussed briefly. Their symptom manifestations will be summarized, along with the evidence, such as it is, that the basal ganglia are involved, at least in expression of symptoms, if not in the root causes. Suggestions for causal explanations, when offered, are done so in a tentative manner. The four disorders considered below are dystonia (10.6.1), Tourette's syndrome and obsessive-compulsive disorder (OCD) (considered together in Section 10.6.2), and attention-deficit/hyperactivity disorder (ADHD) (10.6.3).

10.6.1 Dystonia

Dystonia is a symptom consisting of abnormal involuntary movements, which are relatively slow and long sustained, often affecting axial or proximal muscles, and capable of producing twisting movements and sustained abnormal posture. This reverts to normal in a relaxed state and during sleep (Klawans, 1985). It occurs as a result of a number of primary disorders (Klawans, 1985), which include Huntington's disease (Louis et al., 2000; Mahant et al., 2003), Parkinson's disease (Hallett, 1998), and encephalitis lethargica (as described in Oliver Sacks' *Awakenings*). Dystonia may also arise secondarily, as a result of focal lesions, for instance, in the striatum (especially the putamen), but also in the thalamus, cortex, and elsewhere (Marsden et al., 1985; Rothwell and Obeso, 1987). However, in primary dystonia, no definite brain lesion can be found. A variety of task-specific overuse syndromes, the best known of which is the writer's cramp, may also produce dystonia (e.g., Hirata et al., 2004).

While clear neuropathological evidence is missing in most cases of dystonia, there is some electrophysiological evidence for the involvement of the basal ganglia, based on unit recording in a few patients during neurosurgery. In generalized dystonia, unit firing in both GPi and GPe is low (Lozano et al., 1997; Vitek et al., 1999), suggesting reduced inhibitory tone acting on the motor thalamus. In one patient, it was possible to show that unit firing in GPi fell progressively during repeated fist-clenching, during which the symptom of dystonia gradually increased (Lenz et al., 1998). The reduced firing in GPe and GPi may reflect increased activity in inhibitory links of both direct and indirect pathways from the striatum, without increased activity in excitatory input to these nuclei from STN (as occurs in Parkinson's disease). The involvement of the basal ganglia is also shown by the effectiveness of thalamotomy of the pallidal-receiving thalamic nuclei in relieving the symptoms (Tasker et al., 1988), and also that of pallidotomy (Lozano et al., 1997; Vitek et al., 1999; Ondo et al., 1999). The effectiveness of thalamotomy fits the idea that, as firing

in GPi falls in association with dystonic symptoms, that should in the motor thalamus should rise, and the influence of this be reduced with thalamic lesions. However, the effect of pallidotomy would be to lower even further the inhibitory influence on the motor thalamus, and might be expected to exacerbate rather than improve the symptoms, contrary to what is actually observed. It is also unclear whether the change in pallidal activity is due to a primary abnormality in the basal ganglia, or elsewhere (such as the cortical input to the striatum).

Pharmacological evidence also shows that the basal ganglia can be involved in dystonia. Acute dystonia sometimes follows administration or dose increase of neuroleptic drugs, especially for drugs of high D2-blocking potency or low-cholinergic potency (Jeste et al., 1986). They are the earliest drug-induced syndrome to appear (Marsden et al., 1975). Such an acute syndrome is almost always reversed by anticholinergic agents (Jeste et al., 1986; Klawans, 1985). Ability of neuroleptics to produce acute dystonia largely disappears with chronic treatment (Klawans, 1985). In monkeys, neuroleptics can induce a similar acute dystonia (Gunne and Bárány, 1976), which is decreased by the broad-spectrum dopamine agonist apomorphine or the anticholinergic biperiden (Casey et al., 1980). Paradoxically, both a GABA agonist (muscimol) and an antagonist (picrotoxin), administered subcutaneously, exacerbate the syndrome (Casey et al., 1980).

Longer-term administration of neuroleptic drugs also sometimes leads to a tardive syndrome, whose motor manifestations are indistinguishable from acute dystonia. This is also seen in monkey models of tardive movement abnormalities (Kistrup and Gerlach, 1987). The duration of neuroleptic treatment preceding onset of tardive dystonia is very variable (3 days to 11 years, according to Burke et al. [1982], with a mean of 3.7 years). TD and tardive dystonia are commonly associated in the same patients (van Harten et al., 1997). Like TD, tardive dystonia may persist even for many years after stopping neuroleptic drugs (Burke et al., 1982; Jeste et al., 1986; Wojcik et al., 1991). Therapy is difficult and rarely a complete success. As with TD, expression of the symptoms is sometimes lessened by reinstating neuroleptics, or by giving tetrabenazine (Burke et al., 1982). As with TD, clozapine is favored as a treatment (Lieberman et al., 1991; Adityanjee et al., 1999).

Tardive dystonia is thus similar in some ways to TD, especially in its relation to dopamine-blocking drugs. This suggests that the symptoms arise from abnormal processes in the basal ganglia. However, a number of features suggest that the processes leading to tardive dystonia are different from those underlying TD. The body segments in which tardive dystonia preferentially occurs differ from those for TD. Tardive dystonia tends to occur in young men, while TD is more common in older women (Giménez-Roldán et al., 1985; Yassa et al., 1989). The chances of recovery are worse for tardive dystonia than for TD. The former seems to develop more rapidly than severe TD, requiring fewer months of neuroleptic treatment and a lower cumulative dose (Yassa et al., 1989; Adityanjee et al., 1999). The severity of dystonic symptoms is not related to duration of neuroleptic treatment (Burke et al., 1982). There is a suggestion that a history of prior acute dystonia is more common in those who later developed tardive dystonia (Sachdev, 1993a,b). Phenomenologically, tardive and acute dystonia are very similar, while the movements of TD are quite different from the acute extrapyramidal symptoms, which predispose to later development

of TD. In contrast to TD, anticholinergic agents sometimes alleviate tardive dystonia (Burke et al., 1982; Wojcik et al., 1991). Dystonias of very similar type may occur in Parkinson's disease, and can occur either spontaneously or during L-DOPA treatment (Marsden et al., 1975; Hallett, 1998). In treated patients, the symptoms may occur in either the off- or the on period (Dowsey-Limousin, 2003), and be either improved or worsened by L-DOPA (Jankovic and Tintner, 2001). These facts do not fit easily into the body of knowledge acquired about disorders of the basal ganglia. Treatments very different from those mentioned above are sometimes effective for tardive dystonia, such as electroconvulsive therapy (Kwentus et al., 1984; Adityanjee et al., 1990), or injection of the affected muscle groups with botulinum toxin (Jankovic, 2004). Moreover, dystonias may arise without identified neurological disorder, as a variety of overuse syndromes, such as writer's cramp.

These facts suggest that there are processes at work additional to and unrelated to disorders of the basal ganglia. One possibility is that a pathological reorganization of sensory and motor representation in cortex and thalamus may occur to produce dystonia (Lenz et al., 1999), a suggestion based on the finding that in dystonic patients studied during thalamotomy operations, sensory and sensorimotor maps in the relevant thalamic nuclei are abnormal (see also Hirata et al., 2004). Indirect evidence suggests that overactivity of motor thalamic neurons may accompany dystonia. Bicuculline injected into the motor thalamus of normal monkeys, which would be expected to cause a general overactivity of neurons, produces reversible dystonic postures (Guehl et al., 2000; Macia et al., 2002). One common theme for dystonia may then be indiscriminate overactivity of motor thalamic neurons, producing coactivation of agonists and antagonists. There is no evidence that this coactivation is the result of loss of inhibition at the spinal level, as may apply to parkinsonian rigidity (Obeso et al., 1985). However, dystonia is relieved by thalamotomy in less than a half of cases (Andrew et al., 1983; Cardoso et al., 1995).

Quite apart from involvement of the basal ganglia, there is evidence of abnormal cortical sensory processing in dystonia. Hallett (1995) draws attention to this, and especially to the various "sensory tricks" used to alleviate the abnormal movement for all forms of dystonia. For instance, light touch of the affected part may relieve the spasm. Abnormal sensory input (e.g., resulting from trauma) can also herald the start of dystonia. In idiopathic dystonia, temporal aspects of somatosensory discrimination are impaired (Tinazzi et al., 1999), and in a functional imaging study (Ceballos-Baumann et al., 2004), the prefrontal cortex was found to be overactive and the motor cortex underactive. Impairment in temporal and spatial aspects of sensory discrimination have also been seen in writer's cramp (Sanger et al., 2001). In task-specific dystonia, experiments using transcranial magnetic stimulation show that there is a shift in the balance between inhibition and excitation in the cortex, in favor of the latter (Ridding et al., 1995b; Ikoma et al., 1996; Filipovic et al., 1997; Chen et al., 1997). In an animal model of task-specific dystonia (Byl et al,. 1996, 1997), two monkeys were required to maintain an attended grasp on a handgrip, which repetitively and rapidly (over ~20 ms) opened and closed over a short distance. This was continued for 1100–3000 trials. Toward the end of this training, fine movement control was disturbed in both monkeys and there was a dedifferentiation of receptive fields in cortical somatosensory area 3b, with increase in field size by

10–20 times, and a marked increase in overlap between adjacent representations of the forelimb surface.

In summary, dystonia has many causes. Although, in some cases, there is evidence that the basal ganglia are somehow involved, it is probable that the essential abnormality giving rise to the defining symptoms is some aspect of the physiology of the cerebral cortex rather than the basal ganglia. Alternatively, the balance between cortex and basal ganglia may be abnormal, so that generalization rather than differentiation prevails.

10.6.2 Tourette's Syndrome and Obsessive-Compulsive Disorder

Included among the disorders of "executive function," as defined in Section 1.2 of this work, are Tourette's syndrome and obsessive compulsive disorder (OCD). In terms of phenomenology, genetics, or common comorbidity, there appear to be principles in common between these two. It has been proposed that they reflect dynamic dysfunction of the basal ganglia and connected regions of the overlying anterior part of the cortex. The exact nature of this dynamic dysfunction, and whether it has its roots in the basal ganglia, the cortex, or the balance between the two, are at present unresolved questions. This subsection discusses them briefly, with only tentative conclusions.

The phenomenology of Tourette's syndrome has been described in recent reviews by Albin and Mink (2006) and Shavitt et al. (2006). The hallmark of this disorder is the production of repetitive stereotyped fragments of behavior referred to as tics. Tics may be either motor or vocal. They range from simple tics (contraction of individual muscles, eye blinks, nose twitching, head jerking, mouth opening, throat clearing, etc.) to complex tics (head shaking, scratching, touching, throwing, hitting, gestures, and uttering phrases). Sometimes they reflect disinhibition (performance of normally inhibited acts, such as uttering profanities). Tics fluctuate in type, frequency, and distribution over time. Like dyskinesias, they are exacerbated by stress and reduced by other concurrent motor activity (perhaps for same reasons; see Section 10.3). They are said to be "involuntary." However, this may be questioned, since their expression is preceded by subjective "premonitory urges" (Leckman et al., 1993), which can be resisted in the short term. Performance of the tic then leads, for a brief period, to a subjective sense of relief ("just right" perceptions, according to Leckman et al., 1994), before the urge is reawakened. Premonitory urges and the relief experienced after performance of an act are not in themselves abnormal, since, in many circumstances neurologically normal people experience similar urges to perform some act (the experience of "impatience"). However, the tics themselves serve no purpose and are not integrated into larger patterns of behavior. They can thus be regarded as pathologies of intention or of voluntary action.

Tourette's syndrome is more common in males than females. It tends to run in families (Hyde et al., 1992), and it has been suggested that its inheritance is relatively simple, determined by a single dominant gene with varying penetrance (Robertson, 1989). Tics start during childhood, are maximal in preadolescence, tending to decline, or even disappear by early adulthood (Peterson, 1996). In terms of phenomenology, genetics and relation to age, Tourette's syndrome is a relatively well-defined abnormality, though varying widely in severity, with many cases being so mild as normally to escape notice (Albin and Mink, 2006).

OCD has features in common with Tourette's syndrome. In terms of phenomenology, it is characterized by recurrent unwanted thoughts (obsessions). These obsessions often focus on the fear of acting contrary to the patient's own value systems and are commonly accompanied by anxiety (Rasmussen and Tsuang, 1986). They are often accompanied by persistent ritualized acts (compulsions, such as repeated checking, hoarding, and hand washing). Performance of these ritualized acts leads temporarily to abatement of the obsessive thoughts and decrease of anxiety, just a performance of tics in Tourette's syndrome transiently decreases the premonitory urges. OCD overlaps with Tourette's syndrome both in individuals, and, genetically, in families (Cummings and Frankel, 1985; Hounie et al., 2006). In view of this, it is plausible to regard OCD as involving processes in the basal ganglia similar to those for Tourette's syndrome, but expressed via different functional circuits. Thus, OCD may involve a disturbance in the pathways through the basal ganglia controlling overall focus of attention for goal-directed programs of action, rather than those controlling small-scale acts (as in the case of Tourette's syndrome). Despite these similarities, OCD differs from Tourette's syndrome in its gender distribution (somewhat more common in females than males) and the age distribution (onset most commonly in teenage years rather than childhood, with the disorder commonly persisting into adulthood) (Rasmussen and Tsuang, 1986). There are also differences in the pharmacology of the two disorders (see later this section).

The phenomenology of these disorders indicates abnormality in the process of choice of action or focus of attention, that is, a disorder in executive functions. This suggests that the basal ganglia are involved in these disorders. This proposal is supported by more direct (though inconsistent) evidence of many types. Structural MRI has shown volume abnormalities in the striatum. Some studies find it to be larger than normal in OCD (Scarone et al., 1992; Pujol et al., 2004; but see Szeszko et al., 2004). In Tourette's syndrome, the striatum is reported to be decreased in size (Peterson et al., 1993, 2003) or to have abnormal left/right asymmetry (Hyde et al., 1995; Yazgan et al., 1995). A single postmortem study comparing three Tourette's syndrome brains with control brains claimed that there was a deficit in the Tourette's brains in the number of GABAergic striatal interneurons (Kalanithi et al., 2005). In terms of psychomotor function, "habit learning" (for which the basal ganglia is critical) has been found to be impaired in children with Tourette's syndrome (Marsh et al., 2004), and procedural learning is likewise impaired in OCD (Joel et al., 2005). However, in a study of pursuit-rotor tasks, a typical procedural learning task, learning was reported to be faster than normal in OCD (Roth et al., 2004).

More consistently, a number of papers suggest that the striatum (or parts of it) receive greater-than-normal dopaminergic innervation in some of these syndromes. Such work includes, in Tourette's syndrome, a postmortem study (Singer et al., 1991), and brain-scanning evidence of elevated levels of the dopamine transporter (an indicator of dopaminergic innervation) (Malison et al., 1995; Müller-Vahl et al., 2000; Albin et al., 2003; Cheon et al., 2004; Serra-Mestres et al., 2004; but also see Meyer et al., 1999; Stamenkovic et al., 2001). Similar elevated levels of the dopamine transporter have been reported in OCD (Kim et al., 2003; van der Wee et al., 2004). Elevated levels of dopamine synthesis (Ernst et al., 1999), or dopamine release by stimulants (Singer et al., 2002) have been reported in Tourette's syndrome. A mouse

model of Tourette's disorder/OCD has been developed, in which there is excess striatal dopamine innervation, and a tendency to excessive performance of stereotyped patterns of action (Berridge et al., 2005).

Much of this evidence suggests overactivity of striatal dopamine in these syndromes. Exactly how this might be expressed is unclear, since an excess of dopamine transporter might indicate either an excessive innervation and dopamine-release potential, or faster-than-normal removal of dopamine from extracellular spaces (effectively abbreviating the influence of dopamine). In addition, the evidence is in some ways equivocal. In groups shown to have excessive dopamine transporter density, there is usually considerable overlap with control groups. Hesse et al. (2005) report *reduced* levels of the dopamine transporter in OCD. Sometimes, in Tourette's syndrome, tics are exacerbated, rather than alleviated during neuroleptic treatment, in association with akathisia (Weiden and Bruun, 1987). Dopamine-blocking neuroleptic drugs are useful therapy for Tourette's syndrome (Dure and DeWolfe, 2006), but are not favored as treatment for OCD, where serotonin uptake inhibitors are preferred (Swedo and Leonard, 1994). Tourette's syndrome may occur in combination with attention deficit/hyperactivity disorder (see Section 10.6.3). Stimulants rather than neuroleptics are the recommended treatment for the latter condition, but when the two conditions occur together, the stimulant does not exacerbate the tics (Gadow and Sverd, 2006).

The basal ganglia function in interplay with other parts of the forebrain, especially the anterior regions of the cerebral neocortex. The evidence just cited has to be set alongside evidence of functional abnormality in other parts of the basal ganglia-thalamo-cortical circuitry. Functional imaging has shown a variety of effects in these disorders. Usually, there are changes in functional activity, which encompass various parts of the basal ganglia-thalamo-cortical circuits. Elevated or (sometimes) lowered levels of neural activity are seen in cortical, striatal, or thalamic regions in OCD (e.g., Mataix-Cols et al., 2004; Lacerda et al., 2003) and Tourette's syndrome (e.g., Eidelberg et al., 1997; Adams et al., 2004). In one study of OCD, different regions showed increased neural activity in association with different symptoms (Mataix-Cols et al., 2004), implying that different functional circuits were engaged for each symptom. However, since several connected parts of the basal ganglia-thalamo-cortical circuitry are usually implicated together in functional imaging studies, it is difficult to use such evidence to unravel the basic neural processes underlying the disorders.

There have also been many structural imaging studies of these disorders. Among this evidence are reports of above-normal size of some cortical areas in Tourette's syndrome (Peterson et al., 2001) and OCD (Szeszko et al., 2004). For Tourette's syndrome, there are several reports of above-normal area of the corpus callosum (Baumgardner et al., 1996; Moriarty et al., 1997; Plessen et al., 2004; but see Mostofsky et al., 1999), or of the proportion of white matter in frontal regions in one study (Fredericksen et al., 2002), but not another (Kates et al., 2002). Above-normal white matter volume has also been reported in OCD (Atmaca et al., 2006). A study based on signal intensity in MRI, provided evidence suggestive of above-normal myelination in frontostriatal pathways, and parts of the callosal genu (MacMaster et al., 1999). In psychophysiological terms, there are reports of increased excitability or reduced

inhibitory processes in the cortex (Zieman et al., 1997; Rossi et al., 2005), and increased amplitude and reduced latency of P300 potentials in OCD (Mavrogiorgou et al., 2002), implying accelerated attentional and cognitive processes.

If increased striatal dopamine innervation was a critical aspect of neuropathology in Tourette's syndrome, one would expect there to be an exaggeration of normal aspects of goal-directed habit formation. It is hard then to understand why the tics occur without relation to the normal goals of behavior. In OCD, the compulsions are fragments of behavior with relevance to basic motives, and subjectively produce temporary relief from anxiety associated with these motives, but are emitted without objective fulfillment of any such motive, and recur without objective reactivation of any motivational need. One of the suggested formulations of OCD in neuropsychological terms is that there is an impairment in choosing between immediate reward and long-term goals, emphasis on the former preventing longer-term planning (Cavedini et al., 2006). These descriptions identify the two disorders as psychopathologies of executive functions, but not as exaggerations of dopaminergic reinforcement.

Since these disorders are of childhood/adolescence onset, and may be most severe at these ages, they can be viewed as developmental disorders. During childhood and adolescence, there is an overexuberance of connections, which is reduced during the transition to adulthood. This general statement applies to dopaminergic innervation of the striatum, which appears to be at its peak in early adolescence (Haycock et al., 2003). The supposed hyperinnervation of the striatum in the disorders considered above may thus indicate an exaggeration of a normal process. However, as just discussed, this is not an adequate explanation of the abnormalities in executive functions. Unlike L-DOPA-induced dyskinesias, the symptoms tend to decline in adulthood, and may spontaneously remit. This suggests that they have a basis quite different from that of these dyskinesias. Cortico-cortical connections also undergo reduction in adolescent years from a peak at age about 12 years. An alternative developmental account of these disorders can then be suggested, that the normal preadolescent exuberance of cortico-cortical connections is exaggerated to an abnormal degree. Although the evidence is far from consistent, and cannot be reviewed in detail here, there is some evidence for this suggestion, in that, cerebral gray and white matter volumes in some regions, and callosal cross-section area have been reported to be above normal in these disorders. That the disorders considered here last for several years suggests that they might have a stable morphological basis rather than a dynamic neurochemical one.

How might this suggestion lead to the symptoms of these disorders? In Section 2.2, the unfolding of a normal program of goal-directed behavior was conceived as the dynamic engagement of an "inward spiral," each circuit a round the spiral involving basal ganglia-thalamo-cortical circuits. A normal program of behavior would then start with broad decisions about long-term goals, including activation of particular motives and attentional foci, leading to strategic objectives, and ending with tactical decisions followed by immediate goal fulfillment. There are morphological requirements for such a scheme, based on the patterns of connectivity around the circuits between basal ganglia and cortex. The striatal region dealing with a particular stage of the "inward spiral" should control cortical regions, which project not only to the same striatal region, but also to the striatal region dealing with the

next stage of the inward spiral. Such a principle of organization has been advocated by Joel and Weiner (2000), who refer to "closed loops" (where the striatum is connected to cortical regions that project back to the same striatal region) and "open loops" (where the projection returns to a different striatal region). One might envisage, in normal circumstances, that cortical regions or cell groups exerting direct control over simple or complex acts, project partly to striatal regions which feed forward to the same cortical regions or cell groups, and partly to other regions. The former connections would be expected to mediate repeated items of behavior, or, if the indirect pathway is involved, the maintenance of a state of nonresponding (for instance, in tasks involving a delay). The latter would be implicated in transition to the next stage of a behavioral sequence, or, in delay tasks, in production of the required response to an "imperative signal."

If there is overexuberance of connectivity, in the cortico-striatal, thalamo-cortical or cortico-cortical parts of the circuits, the proper operation of this scheme of organization may be subverted. In Tourette's syndrome, because of superabundant connectivity (perhaps in the cortico-striatal pathway), cortical regions might project more strongly than normal to striatal regions projecting back to the same cortical area. There is then the possibility of closed loops of connections becoming completely dominant, such as seldom occurs in normal development. The result is that simple or complex motor acts occur repetitively, unintegrated with overall strategies of behavior (i.e., simple or complex tics). At a higher level, a similar description might fit the obsessions and compulsions of OCD. This account fits with some studies which show that in OCD, there is a difficulty in organizing extended strategies of behavior, for instance, in variants of the "Tower of Hanoi" task (van den Heuvel et al., 2005). OCD patients have also been found to be impaired in generating novel sequences of responding, even after extensive training (Chamberlain et al., 2006). Such impairments would be expected if, because of extra-strong closed loops of connections, subjects could not escape from repetition of stereotyped behaviors.

Under normal circumstances, performance of each motor act may fulfill the intended goal of that act, subjectively registered as "relief" from the state of tension arising from an incomplete action. The "sense of control" may actually be accompanied by a dopaminergic signal to reinforce the relation between the act and its consequences. If however, neural activity in the cortical region is followed not only by the act, but also activation of circuits through the basal ganglia which promote recurrence of the act, that subjective state of tension would be reinstated repetitively as the act is repeated. Similar statements (but involving different cortical and striatal regions) can be made for the relation between obsessive thoughts and the compulsions in OCD. In either disorder, dopaminergic tone may be expected to enhance the abnormal behavior, so that dopamine blockers alleviate the symptoms, but this is not in itself a specific part of the pathology, since dopamine activates most forms of active behavior.

10.6.3 Attention Deficit Hyperactivity Disorder

Attention deficit hyperactivity disorder (ADHD) is characterized phenomenologically by three abnormalities: difficulty in sustaining attention, impulsiveness of

responding to immediate events, and (sometimes) hyperactivity (Goldman et al., 1998). It is highly heritable (Thapar et al., 1999), starts in childhood, and, although declining during adolescence, sometimes endures in modified form into adulthood. It often shows comorbidity with Tourette's syndrome (Spencer et al., 2001; Pringsheim et al., 2003; Denckla, 2006), although in some respects, it is the diametric opposite of this condition. In particular, the favored drug therapy is a stimulant which blocks dopamine reuptake (methylphenidate), rather than a dopamine antagonist. Nevertheless, levels of the dopamine transporter have been reported to be elevated in this disorder (Dougherty et al., 1999; Dresel et al., 2000; Krause et al., 2000, 2005; Cheon et al., 2003; but see van Dyck et al., 2002) just as they are in Tourette's syndrome and OCD. This has led to the suggestion that, as dopamine is removed more rapidly from the extracellular spaces, the delay-of-reward gradient becomes steeper, with hyperactivity as a compensatory response (Castellanos and Tannock, 2002). However, the normal rate of removal of dopamine is much faster than the delay-of-reward gradients in relevant behavioral tests, which makes this model implausible.

Another way in which the brain in ADHD disorder is the opposite of that in Tourette's syndrome and OCD is that volumes of white and gray matter in the hemispheres are generally found to be reduced rather than increased (Filipek et al., 1997; Semrud-Clikeman et al., 2000; Overmeyer et al., 2001; Kates et al., 2002; Mostofsky et al., 2002; Hill et al., 2003; Durston et al., 2004; Carmona et al., 2005; Seidman et al., 2005). The best-defined hemispheric white matter tract, the corpus callosum, has been reported to have decreased cross-section area in ADHD in several studies (Hynd et al., 1991; Semrud-Clikeman et al., 1994; Giedd et al., 1994; Baumgardner et al., 1996; Hill et al., 2003). A few reports disagree: Sowell et al. (2003) found *enlarged* gray matter volumes in some regions, and Carmona et al. (2005) could detect no decrease in white matter volumes. If white matter volume *is* below normal, this could indicate a reduction in the number of axons, their mean caliber, or their degree of myelination. One study using diffusion tensor imaging, showed reduced anisotropy in cerebral white matter (Ashtari et al., 2005), which can be interpreted as a consequence of reduced mean axonal caliber (Miller, 2004). The evidence on these questions is currently unclear since one study (Pueyo et al., 2003) finds indications, from MR signal intensity, of higher-than-normal myelination in right frontal regions in ADHD, and another study finds faster-than-normal interhemispheric transmission time via the corpus callosum (Brown and Vickers, 2004).

Decreases in white matter volume, associated with decreased myelination and/or mean axonal caliber may apply just to particular white matter pathways. If either of these occurs, axonal conduction time in the affected pathway will be increased, and so also will be the spread of conduction time in a population of axons in that pathway. Hence, the effectiveness of postsynaptic convergence, needed to fire a neuron will be reduced.* Were this to occur in the cortico-striatal pathway in ADHD, the potency of transmission would be reduced, and reinforcing actions of stimulant medication might be needed to restore transmission toward normal levels (as is the case).

* Theoretical reasoning relating a relative absence of rapidly-conducting axons in the cerebral hemispheres to a wide variety of psychological and psychophysiological processes is presented, in the context of an overall theory of schizophrenia, in another work (Miller R., *A Neurodynamic Theory of Schizophrenia and Related Disorders*. In Preparation).

The fact that the symptoms of ADHD often abate during the transition to adulthood fits this proposal, since myelination of hemispheric axons normally reaches completion only at this stage, and a similar process of maturation, albeit delayed, may be expected in ADHD. How such a pathology might impact on behavior is not clear, but since the reduced effectiveness of transmission would probably apply to neurons of origin of both the direct and indirect pathways, behavioral activity need not be globally reduced, and might be increased. Purposeless activity, unfocused on any goal might be the result.

11 Synopsis of Part II and Predictions Derived from It

Part II of this monograph gives an account of the symptoms of disorders of the basal ganglia, which is far from complete. It has concentrated on syndromes where the pathological basis is well established, or which can be plausibly postulated. Many other disorders, on the borderland between neurology and psychiatry, arise in the basal ganglia, but their basis, whether in cell loss or in more functional abnormalities, is not yet clear. For the syndromes, which *are* considered, there are important details yet to be discovered relating the exact region of cell loss or disturbed neuronal dynamics to specific types of symptoms. One indication of this comes from the use of deep brain stimulation for treatment of Parkinson's disease: Krack et al. (1998) report that, even within a single structure, such as GPi, there are precise topographic relations between the site stimulated and the symptoms alleviated (i.e., rigidity and dyskinesia versus akinesia). A detailed interpretation of such findings is not possible at present, partly because the basic mechanism by which deep brain stimulation alleviates parkinsonian symptoms is uncertain. Another indication from clinical studies of additional complications to the basal ganglia is that, sometimes, lesions to GPi, far from alleviating parkinsonian symptoms, may actually cause akinesia (Bhatia and Marsden, 1994).

Beyond this, some general features emerge concerning symptoms of basal ganglionic disorders. From the preceding theory of normal functions of the basal ganglia (Part I), it might have been anticipated that symptoms of these disorders are a direct result of breakdown of the special organizational features of the basal ganglia—especially, a breakdown of the specificity of connections, or of the functional specificity shown in their dynamic operation. In part, this is true: The symptoms of Huntington's disease reflect loss of the capacity to "turn on" voluntary movement or to "turn off" unnecessary accessory movement. In Parkinson's disease, major symptoms—festination, akathisia, some aspects of akinesia—other than the classic ones of rigidity and tremor can be seen as loss of behavioral selectivity, consequent on the widespread overactivity of striatal neurons. A variety of evidence (psychological and electrophysiological) also indicates that in Parkinson's disease, there is a loss of specificity in the targeting, by the basal ganglia, of discrete cell assemblies in the CTH network. All these symptoms can be seen as dysfunctions of the primary function of the basal ganglia in behavioral selection and attentional focus.

Disorders of the basal ganglia also result in prominent motor symptoms, which present difficulties for the proposal that the basal ganglia are primarily involved in behavioral selection rather than motor control. However, it appears that many

of the classic motor symptoms of Parkinson's disease arise in a somewhat indirect manner, from special details of the abnormal dynamics of the basal ganglia, rather than from their central characteristics. These complications would have been difficult to predict from the basic features of the theory of the basal ganglia presented here. In particular, the fact that the subthalamus is excessively active in Parkinson's disease (probably due to removal of a direct dopaminergic inhibitory influence) is a major factor leading to these classic symptoms. Parkinsonian tremor is one example of such a symptom. It is expressed by relay of abnormal neural activity through the motor thalamus. It is proposed that the combination of excessive inhibition from the striatum and excessive excitation from the subthalamus leads to burst firing in the pallidum, which is sometimes rhythmic, and can then be entrained in long-loop resonance involving the thalamus, the peripheral motor apparatus, and sensory feedback from it. Parkinsonian akinesia probably arises in part from excessive inhibition (derived from overactive neurons in GPi) directed at brain-stem structures such as the pedunculopontine nucleus, which normally promotes automatic motor routines. The basis of parkinsonian rigidity is incompletely understood, but is probably also expressed via this brain-stem nucleus, and its control of muscular tone via circuitry in the spinal cord.

Dopamine-dependent psychosis is caused in an immediate way by excessive impulse traffic in the meso-striatal dopaminergic pathway (whose earlier causes, probably many and varied, are not dealt with here). Although there are motor dysfunctions associated with psychosis, or dopaminergic overactivity produced in other ways, the primary symptoms are in the cognitive realm. The salience of mental images is generally enhanced by the excessive operation of the reinforcement function of dopamine. Sometimes, this leads to abnormalities that are not distinctively psychotic. However, when subliminal perceptual images are amplified to the point where they seem like external perceptions, or when the motivational significance of beliefs is exaggerated and distorted, hallucinations and delusions of distinctly psychotic proportions occur. Mechanisms akin to normal dopamine-dependant learning are entrained during the active phase of psychosis, so that there is progressive elaboration of delusional systems. Mechanisms of enduring memory are also entrained, which make recovery, especially from the symptom of delusions, much slower than would be expected on purely neurochemical grounds. This model of psychosis is based on the role of dopamine in synaptic modification occurring in the striatum. However, paradoxically, it is well established that this process relies on actions of dopamine at D1 receptors, not the D2 receptors held to underlie therapy with antipsychotic drugs. A resolution of this paradox is suggested in the proposal that D2-blocking antipsychotic agents act indirectly, their ultimate target being the reduction of intracellular formation of cAMP, upon which dopamine-dependent synaptic modification is based. A previous hypothesis about the details of this indirect action, supposedly mediated by changes in firing rate of midbrain dopamine neurons, is refuted by new evidence. Instead, it is noted that D2 blockers lead to increased ACh release in the striatum. This, it is proposed, activates muscarinic M4 receptors on striatal principal neurons, leading to reduction in cAMP formation. It is suggested that this sets in motion the therapeutic process with typical neuroleptic drugs.

A number of syndromes arise as complications of some of the above disorders, where there has been prolonged underactivity of striatal dopamine function. These include neuroleptic-induced tardive dyskinesia, peak-dose dyskinesia in parkinsonian patients treated with L-DOPA, and neuroleptic-induced supersensitivity psychosis. All three syndromes, once established, are rather persistent, or even permanent. Arguments are presented that the basic pathology underlying these syndromes is loss of striatal cholinergic interneurons. These neurons normally play an important modulatory role in the striatum, and it is suggested that they are necessary to prevent an uncontrolled positive feedback of activity circulating between basal ganglia and neocortex. It is proposed that such interneurons are damaged and destroyed, in states of chronically lowered dopaminergic tone, due to their having to sustain excessive activity for long periods (months or longer). When they are lost, symptoms may appear in high-dopamine states, which would seldom appear otherwise. These symptoms may be in either the domain of abnormal movement (dyskinesia) or of abnormal thoughts (psychosis). Some information available on the exact phenomenology of tardive and peak-dose dyskinesias suggest close parallels with psychosis, especially in their temporal features. These dopamine-dependent dyskinesias can, thus, be regarded as "psychosis of bodily movement." Since, according to the model proposed, drug therapy for psychoses normally depends on the integrity of the striatal cholinergic interneurons, which, it is suggested, are lost or damaged when tardive dyskinesia or supersensitivity psychosis emerges, one can explain why these syndromes, in severe cases, are no longer treatable with classic neuroleptic drugs. Cases of refractory psychosis, which arise for reasons other than prolonged dopamine underactivity may have a similar pathological basis. Detailed evidence on the receptor pharmacology of TD and PDD is not completely consistent. The majority of it, however, suggests that expression of these two dyskinetic syndromes is enhanced by D1 agonists and attenuated by D1 antagonists. Agonists at D2 receptors usually do not exacerbate these dyskinesias, unless the patients, or animals in primate models of the disorders are "primed" by at least one experience of L-DOPA leading to dyskinesia. A limited body of information is also suggestive that agonists at M4 muscarinic receptors may alleviate these dyskinesias. These pharmacological findings support the idea that the dopaminergic dyskinesias arise by processes closely parallel to those leading to psychosis.

Comparing the different movement disorders surveyed here, one can see a progression from normal purposive voluntary movement to the seemingly random and quite purposeless movements of hyperkinetic Huntington's disease. Two intermediate stages are: "punding" in otherwise normal subjects who abuse stimulant drugs in very high doses, where purposeful behavioral routines are performed aimlessly and repetitively, and dopaminergic dyskinesias. In terms of the dynamics of the striatum in these various stages, it is likely that local striatal inhibition completely suppresses unwanted accessory movements in the normal situation. During punding, this inhibition still occurs, but the few neurons that are active are excessively so, with the result that behavioral stereotypy prevails, irrespective of fulfillment of any goal. In dopaminergic dyskinesias, the increase in striatal unit activity is greater, and uncontrollable sequences of neural activity occur. In principle, these may include once-purposeful elements, but occur in such profusion that the overall aim is lost

(a process similar to that occurring in the cognitive domain in psychosis). It is not clear to what extent the dyskinetic movements themselves are fragments of once truly-purposeful behavior; some may be truly purposeless motor acts, arising by "adventitious reinforcement" when dopaminergic tone is high. In hyperkinetic Huntington's disease, there is a mixture of normal purposeful activity and normally suppressed, but essentially random accessory movements, the latter coming to predominate as the disease progresses. In Huntington's disease, and possibly, but to a lesser extent, in advanced Parkinson's disease, loss of principal striatal neurons may account for the loss of purposeful movements and their replacement by random ones.

Section 10.6 dealt with a number of disorders (dystonia, Tourette's syndrome, OCD, and ADHD), whose basic pathology is not clear, although it is very likely that the basal ganglia are involved, even if not as the primary site of abnormality. Tentative suggestions are made, generally focusing on patterns of connectivity outside the basal ganglia, or afferent to the striatum, or balance between cortex and basal ganglia rather than on pathology in the core nuclei of the basal ganglia.

With the exception of these disorders, the source of symptoms in the disorders covered in Chapters 7–10 are summarized in Table 11.1 below. This table shows the original cause of each symptom in cell loss, or dopamine blockade or overactivity, the clinical condition with which this is associated, whether the symptom reflects abnormality in the direct or the indirect pathway from the striatum, and which functional circuits through the basal ganglia are primarily involved (viz, those involved in "microbehavior," "macrobehavior," or in the higher-level circuitry for cognitive processes, or selection of motivational or attentional focus).

A number of predictions were made in Part II, summarized as follows: In Section 8.7.2, it was suggested that, in akinetic parkinsonian syndromes, neurons in PPN with descending connections should be silenced. In Section 9.5, a major prediction was made that blockers of dopamine D1 receptors might have antipsychotic potency (a proposal widely denied at present). The proposal that TD, PDD, and supersensitivity psychosis arise due to cell loss in the striatum, restricted to the cholinergic interneurons, is supported by much indirect evidence. However, the most incisive empirical tests of this, involving neuropathological study in brains from patients in whom these syndromes had been rigorously defined, is yet to be carried out (see Section 10.2.5). In Section 10.3, a sketchy account of the phenomenology of movement disorders in TD and PDD was given, in support of a number of predictions from theory. There is room for much further observational work to amplify these anecdotes.

Several topics are not resolved here: At the level of basic neuroscience, the mechanisms by which underactivity of the dopamine system in the striatum leads to widespread overactivity of the principal neurons is not fully known. It may depend on excessive activity in the cholinergic interneurons, but the mechanism by which this leads to enhanced impulse firing in the principal neurons is only partially known. In the clinical domain, several questions are at present unanswered, such as the level of impulse activity in neurons of the motor thalamus in various conditions and its theoretical significance, the complex field of dystonia, and the question of why dyskinesias especially those of TD have a preference for oro-facial musculature. Further, clarification of the basis of parkinsonian rigidity

TABLE 11.1
Synopsis of Postulated Origin of Major Symptoms of Disorders of Basal Ganglia

			Symptoms		
Pathology/or Other Cause	**Disorder**	**Pathway/Structure**	**MicroB**	**MacroB**	**Cogn/Att**
Loss of striatal projection neurons	HD (early)	Indirect cell loss (G) (direct p/w unopposed)	Chorea, athetosis, ballismus	?	Psychiatric symptoms ("irritability": release of proscribed behavior)
	HD (advanced)	Direct cell loss (G)	?	Akinesia	? Dementia
Loss of DA innervation	PD	Direct p/w overactive (G)	?	Festination, akathisia, "pulsion"	Cognitive aspects of gait control
		Indirect p/w overactive (G)	?	Akinesia	?
		Subthal overactive	Tremor, rigidity	Akinesia	? Blocking of thoughts
Blockade of D2 receptor	NLD treatment	Direct p/w overactive (G)	?	Akathisia	?
		Indirect p/w overactive (G)	?	Akinesia	?
		Subthal overactive	Rigidity, catalepsy (rats)	Akinesia	–
Dopamine overactivity	Stimulant intoxication	Direct p/w overactive (S)	"Choreiform movements" (R)	Stereotypy, "punding"	Psychosis (delusions, etc.)
		Indirect p/w overactive (S)	?	? "High-dose" stereotypy (rats)	?
	Psychotic illness	Direct p/w overactive (S)	?	Stereotypy	Delusions, etc.
		Indirect p/w overactive (S)	?	?	? Thought blocking, some negative symptoms
Dopamine overactivity + ACh cell loss	Advanced PD with L-DOPA treatment	Direct p/w overactive (S)	Peak-dose dyskinesia	?	L-DOPA-induced psychosis
		Indirect p/w overactive (S)	"Off" phase of "on-off" effect	?	?
	Prolonged NLD treatment	Direct p/w overactive (S)	Tardive dyskinesia	?	Supersensitivity psychosis

Note: Cogn/Att = Symptoms in the cognitive domain, or in selection of focus of attention; G = general (loss of, or overactivity of striatal neurons); HD = Huntington's disease; MicroB = "microbehavior" (i.e., limited to simple movements); MacroB = "macrobehavior" (i.e., involving organized whole-body programs of behavior); NLD = neuroleptic drugs; p/w = pathway; R = refer to paper of Rylander (1972); and S = specific (overactivity of striatal neurons).

is also needed. Furthermore, the effects of deep brain stimulation in Parkinson's disease and other disorders of the basal ganglia is not incorporated in the theory presented here, because the immediate effect of such stimulation, that is, whether it enhances or inhibits neural activity at the stimulation site, and how this is achieved, is unclear. The tentative suggestions made in Section 10.6, for the basis of several less well-understood disorders require much further investigation before they can be accepted. Despite these substantial areas where understanding is incomplete, it is hoped that the large-scale view of the basal ganglia developed in Part I of this book, and its extension in Part II to cover disorders of the basal ganglia, provides a general framework that will allow further experimental and clinical research as well as theory development to proceed. This should allow the basic premises of the present theory to be assessed, and may also lead to elucidation of the remaining unsolved problems.

Much of this book has been concerned with developing a mechanistic account of what is called "voluntary action." The author is aware that, quite apart from scientific theories, this raises some central questions of philosophical debate. Some philosophers might think that a "mechanistic account of voluntary action" was a contradiction in terms. Certainly, the job of neuroscience *is* to try to produce such a mechanistic account. However, this need not imply a complete and fine-grained determinism in the actions of either humans or animals. Were this to be the case, the concept, central for social life of humans, of an autonomous "metaphysical person", would be severely undermined. Much can be said on this subject, but it is in the realm of philosophy, not science, and these issues must remain unresolved here.

Appendix 1: Abbreviations

ACh: Acetylcholine
ADHD: Attention deficit hyperactivity disorder
cAMP: Cyclic adenosine monophosphate
CCH: Cross-correlation histogram
ChAT: Choline acetyl transferase
CHO: Chinese hamster ovary cells
cRNA: Complementary RNA
CTH network: Cortico-thalamo-hippocampal network
DYN: Dynorphin
EEG: Electroencephalography
EMG: Electromyography
ENK: Enkephalin
EP: Entopeduncular nucleus
EPSP: Excitatory postsynaptic potential
ERP: Event-related potential
GABA: γ-Aminobutyric acid
GP: Globus pallidus
GPe: Globus pallidus, external segment
GPi: Globus pallidus, internal segment
6-HD: 6-Hydroxydopamine
IPSP: Inhibitory postsynaptic potential
ISI: Interspike interval
M1: Primary motor cortex
MD: Mediodorsal nucleus of thalamus
MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
mRNA: Messenger RNA
NMDA: *N*-methyl-D-aspartic acid
OCD: Obsessive-compulsive disorder
PDD: Peak-dose dyskinesia (in Parkinson's disease)
PPN: Pedunculopontine nucleus
RT: Reaction time
RT-PCR: Reverse transcriptase polymerase chain reaction
S1: Primary somatosensory cortex
SNC: Substantia nigra pars compacta
SNR: Substantia nigra pars reticulata
SP: Substance P
STN: Subthalamic nucleus

TD: Tardive dyskinesia
TMS: Transcranial magnetic stimulation
TTX: Tetrodotoxin
VA: Nucleus ventralis anterior of thalamus
VL: Nucleus ventralis lateralis of thalamus
VM: Ventromedial nucleus of thalamus

Appendix 2: Pharmacological Agents and Their Actions

Apomorphine: Agonist at dopamine receptors (both D1 and D2 families)
Bicuculline: GABA antagonist
Ceruletide: Cholecystokinin analog
Clozapine: Atypical antipsychotic drug, effective in refractory psychosis
Fenoldopam: Dopamine D1 agonist
Flunitrazepam: GABA ligand
Flupenthixol: Antipsychotic drug with affinity for both D1 and D2 dopamine receptors
Forskolin: Stimulant of cAMP production
Haloperidol: Dopamine D2 antagonist
6-HD: Neurotoxin specific for catecholaminergic neurons
Ibotenic acid: Glutamate agonist; neuronal excitotoxin
Kainate: Glutamate agonist; neuronal excitotoxin
Kynurenate: Broad-spectrum glutamate antagonist
MPTP: Neurotoxin specific to dopaminergic neurons
Muscimol: GABA agonist
(+)PHNO: Dopamine D2 agonist
Picrotoxin: GABA antagonist
Piribedil: Agonist at dopamine receptors (both D1 and D2 families)
Quetiapine (Seroquel): Atypical antipsychotic drug with similarity to clozapine
Quinelorane: Dopamine D2 agonist
Quinpirole: Dopamine D2 agonist
Reserpine: Depleter of all monoamine transmitters
Ropinirole: Dopamine D2 agonist
RU24213: Dopamine D2/D3 agonist
SCH23390: Dopamine D1 antagonist
SKF38393: Dopamine D1 agonist
SKF81927: Dopamine D1 agonist
SKF82958: Dopamine D1 agonist
Tetrabenazine: Depleter of all monoamine transmitters

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Neuroscience

A Theory of the Basal Ganglia and Their Disorders

Robert Miller

The Basal ganglia, to adopt a phrase of Churchill's, are "a riddle wrapped in a mystery, inside an enigma." And although there is a wealth of information available on them, this research field remains controversial due in part to the diverse number of disciplines involved. **A Theory of the Basal Ganglia and Their Disorders** provides a clear, coherent view of basal ganglia that integrates evidence from the basic neurosciences, neurology, and psychiatry. The author explores the basal ganglia within a context of the function of the mammalian forebrain as a whole.

While many books cover cutting-edge research, none have addressed large-scale questions about the role of the basal ganglia as a whole. Until now. This is arguably the only book published in the last 50 years that has attempted to provide an overall theory of the basal ganglia, as well as relevant areas of neurology and psychiatry. It concisely presents the theory, rather than comprehensively covering all the literature, and places the essential clinical facts within a framework formulated for normal operations of the basal ganglia. Presenting a unified view, the book takes several steps toward unraveling the riddle that is basal ganglia.

Features

- Integrates research from neuroscience, neurology, and psychiatry
- Explores the basal ganglia in the context of the function of the mammalian forebrain as a whole
- Discusses the implications of the theory for treating some of the disorders of the basil ganglia
- Develops a conceptual theory based on the normal function of the basal ganglia
- Details the mechanisms that relate basic pathology to the manifestation of symptoms for related disorders

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