Navigated Transcranial Magnetic Stimulation in Neurosurgery

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Foreword

With the goal to achieve optimal precision and safety in the operating theater, a neurosurgeon must investigate not only the structure and vasculature of the brain but also its neural functions. The human central nervous system (CNS) is the single most complex organ in the known universe, and its functional networks are not yet perfectly understood. In this setting, in order to preserve the quality of life of patients who will undergo brain surgery, it is crucial to study the organization of neural circuits before removal of a part of the CNS affected by a cerebral disease, e.g., epilepsy or tumor. Due to a major interindividual anatomo-functional variability, especially in case of brain lesions, which can induce mechanisms of neuroplasticity, mapping techniques are very helpful to understand the distribution of cortical and subcortical pathways underlying motor, language, cognitive, and emotional functions at the individual level. To this end, intraoperative direct electrical stimulation (DES) in awake patients remains the gold standard to optimize the extent of resection (EOR) while minimizing neurological morbidity. However, even though this method allows real-time anatomo-functional correlations throughout the surgical procedure, in order to detect and to preserve the structures crucial for brain functions, it is also important to benefit from complementary techniques that permit a noninvasive preoperative mapping. Functional neuroimaging has been extensively used in the past decade, but its main limitation is the impossibility to differentiate critical areas which should not be removed during surgery, to avoid permanent deficit, versus regions involved in a neural network but which can be compensated—and thus surgically resected.

In this state of mind, navigated transcranial magnetic stimulation (nTMS) represents an original tool opening new avenues in the exploration of the CNS, especially in brain-damaged patients. Indeed, as intraoperative DES, nTMS offers the unique opportunity to create a transient virtual disruption of neural networks, with the aim to identify the cortical areas crucial for brain functions. However, contrary to DES, nTMS is a noninvasive technique that can be used before surgery to map the eloquent cortex and to plan the resection accordingly. This is the reason why a textbook on nTMS in neurosurgery was desperately needed. Led by the editor, Sandro M. Krieg, this collective body of work will serve as a comprehensive textbook for all physicians with an individualized personal approach of brain surgery. What makes this book so unusual is that it contains all required information to use

nTMS in a department of neurosurgery and outlines pros and cons to other techniques. The approach the authors have taken in defining this new technology and its implication for neurosurgical management are quite unique and innovative, to say the least.

The book is organized in a very logical and informative fashion, starting off with critically important chapters covering the basic principles of nTMS. The clinical aspects are further evoked in chapters on preoperative motor and language mapping. To this end, Dr. Krieg is a master at explaining and detailing how to use nTMS for surgical planning and how to combine this method with other techniques, as fiber tracking. I particularly like the way in which further brain functions can be mapped by nTMS and in which this methodology may be used in children—knowing that it is very difficult to achieve awake surgery in pediatric population, especially under 10 years. Interestingly, the fact that nTMS is also able to modulate neural networks for neurosurgical applications, as previously done in neuropsychiatry for depression, is depicted in a series of detailed chapters on these subjects. For example, nTMS can be helpful to treat chronic pain. In the future, this technique could also be considered to induce and canalize neuroplasticity, allowing an increase of the EOR or even an improvement of the neurological status—for example, by combining it with specific programs of rehabilitation in patients with neurological deficits. Finally, in the field of cognitive neurosciences, nTMS may represent a unique tool to investigate CNS processing in humans. Indeed, thanks to recent advances in the new science of connectomics, which aims to comprehensively map neural connections at both structural and functional levels, coordination of cognitive and behavioral domains is now attributed to parallel and intersecting large-scale neural circuits that contain interconnected cortical and subcortical components. In this context, a technique based on the concept of transitory disruption of neural circuits will undoubtedly provide new insights into the organization of such a networking brain. Yet, it is worth noting that nTMS can achieve only a mapping of the cortex, but it is not able to map the white matter tracts that nonetheless constitute a crucial part of the connectome. From a clinical point of view, preservation of subcortical pathways is essential during brain surgery, because the white matter connectivity is a well-known limitation of neuroplasticity. In other words, currently, nTMS should still be combined with other mapping techniques, especially intraoperative DES, in order to be more extensively validated and to compensate its inability to investigate directly the function of the fibers.

It is crucial for modern clinical neuroscience, and especially for neurosurgery, to incorporate advances in this complex field of brain mapping in as timely a fashion as possible, so that patient care becomes guided by the latest increments of relevant technology and knowledge with regard to CNS processing. I have no doubt that this comprehensive volume edited by Dr. Krieg and his colleagues will serve this purpose with considerable distinction. All in all, this text is a major contribution that

will be significant in the history of neurosurgery and cerebral mapping. If you only have one reference source on nTMS in brain surgery, this must be it!

Montpellier, France Hugues Duffau, M.D., Ph.D.

A Word from the Editor

Seven years ago, our neurosurgical department started implementing nTMS. First, we performed preoperative motor mappings, and then we tried to establish language mapping protocols (using ourselves as volunteers). Finally, we used language mapping to analyze our brain tumor patients. Recently, we began applying nTMS to map other brain functions and using it for therapeutic applications.

At the same time, we have optimized the way that we actually integrate the functional nTMS data into our neurosurgical routine. We started with surgeons, as they had to get used to these data, and then integrated nTMS data in our interdisciplinary tumor board discussions.

By making the data easily available to every physician via integration into our hospital's electronic infrastructure, everyone in the department quickly became used to dealing with nTMS data.

Along with these developments, we engaged in seminal international collaborations that led to highly valuable clinical data and—more importantly—many new friends.

This book is thus the result of our interaction with the international neurosurgical nTMS community. In this way, it serves as a signal to all of us that, in neurosurgery, nTMS research means cooperation with an international community.

In this spirit, each year, our group at TUM has served as a host for numerous guests from all over the world, providing them with training and insights into nTMS research and its clinical uses. In doing so, we have gained many collaborators and friends, as well as unlimited options for scientific exchange.

In the future, we want to welcome even more visitors and to continue establishing a researcher exchange program, which we have already started with some of our closest collaborators.

This book was created through the efforts of a team that is composed of experienced, well-known international experts, making this book an exclusive composition of information about the use of nTMS in neurosurgery, which has not previously been available in any other form. By containing different approaches of various international experts, I did not try to create a consensus for the described stimulation protocols, analysis software, or used nTMS devices. Contrariwise, I welcomed the description of differing approaches by the individual authors in order to make this book a collection of feasible approaches rather than a document of my personal opinion.

Therefore, I want to encourage every reader to provide the team, and me in particular, with criticisms, suggestions, and personal wishes regarding how to further improve this unique collection of information for all those who work in this evolving field.

Sandro M. Krieg, M.D., M.B.A.

Contents

Introduction

Mapping and monitoring of brain function is far from being new. It has always been in the focus of neurosurgeons, i.e., already in the days of Wilder Penfield using awake surgery to map motor and sensory function (Penfield and Boldrey 1937). The reason for this being quite obvious is to completely remove tumors or epileptogenic tissue without hurting the patient. To achieve this ideal goal has stimulated many neurosurgeons ever since, among them myself. In the early stages of my career in the late 1980s, I developed an interest in clinical neurophysiology, focusing on the rather new technique of motor evoked potentials (MEP) (Meyer and Zentner 1992; Barker et al. 1985). This technique triggered a development of monitoring and mapping of motor function in the asleep (anesthetized) patient. Several innovative groups paved the road for the integration of this technique into clinical routine, while simultaneously, awake craniotomy for language mapping and monitoring saw a renaissance (Penfield and Boldrey 1937; Taniguchi et al. 1993; Cedzich et al. 1996; Deletis 1993). Thus, it became part of the neurosurgeons' armamentarium even before studies showed that intraoperative MEP mapping and intraoperative monitoring (IOM) can actually prevent neurological damage (Sanai and Berger 2010; Duffau et al. 2005; De Witt Hamer et al. 2012). Today, IOM and intraoperative MEP mapping via DES are well-established techniques, which according to me are mandatory for the resection of highly eloquent tumors.

More than ever, it has become clear that the aim of surgery of low- as well as of high-grade gliomas and metastases has to be gross total resection (GTR) to achieve the most favorable oncological and functional outcome (Laws et al. 1984; Polin et al. 2005; Stummer et al. 2006). Thus, neurosurgeons were seeking for a proper method, which would preoperatively allow outlining functionally relevant areas for estimating surgical risk and planning appropriate and safe approaches, in short, for being prepared before going to the operating room with our patients.

Preoperative mapping in a noninvasive fashion was for a long time reduced to functional magnetic resonance imaging (fMRI) and magnetoencephalography (MEG) (Sobottka et al. 2002; Tarapore et al. 2013; Leclercq et al. 2010). While MEG requires substantial infrastructure and thus never reached broad acceptance, fMRI was considered the standard for noninvasive mapping of neurosurgical patients for about two decades (FitzGerald et al. 1997). Yet, blood-oxygen-level-dependent (BOLD) contrast as measured by fMRI does not have the required spatial resolution and accuracy especially close to intracerebral tumors because these

tumors severely impair oxygenation and therefore BOLD contrast. As a result, fMRI mapping and intraoperative DES mapping do not correlate sufficiently in the vicinity of brain tumors (Lehericy et al. 2000; Bizzi et al. 2008; Roessler et al. 2005; Giussani et al. 2010). Consequently, there was still no proper methodology available, which reliably provided accurate preoperative noninvasive functional mapping in patients harboring brain gliomas or metastases. The gold standard being invasive mapping was also only available in dedicated centers (i.e., with an epilepsy program) and required substantial logistics (Kral et al. 2006).

Only recently, nTMS was introduced as a new modality for preoperative mapping in neurosurgery. The combination of the "old" accurate method to map motor function via transcranial magnetic stimulation (TMS) (Barker et al. 1985) and neuronavigation has been advanced over the years, resulting in real-time localization of the intracranially induced electric field and its field strength allowing for highly precise noninvasive mapping today (Ruohonen and Ilmoniemi 1999; Ilmoniemi et al. 1999; Picht et al. 2009; Krieg et al. 2012). For the first time, we neurosurgeons now have a tool, which allows us to outline eloquent and noneloquent cortex before surgery with a comparable accuracy to intraoperative DES. By providing such exact data, it changes our clinical practice by allowing functional data to influence patient consultations, surgical approaches, and oncological considerations. While preoperative mapping of motor and language function has already been established, the possibilities of neuropsychological or cognitive mapping are currently further investigated. Their potential, e.g., by guiding intraoperative awake mapping, is rather high.

Additionally to pure functional mapping, navigated repetitive TMS (nrTMS) is also able to modulate function. Besides other therapeutic applications for depression or chronic pain, nrTMS also showed a positive effect on the improvement of aphasia as well as motor recovery in chronic stroke patients in randomized multicenter studies by inducing functional reorganization (Huang et al. 2004; Kim et al. 2006; Takeuchi et al. 2009; Takeuchi and Izumi 2012; Abo et al. 2014; Naeser et al. 2011; Du et al. 2016). Thus, rather than waiting for tumor-induced functional reorganization, the potential of nrTMS-induced spatial functional reorganization in order to move eloquent brain functions away from the planned resection cavity requires further investigation. Its impact, though, would be enormous. However, usually progress in clinical science comes in small steps. It is clear now already that nTMS is one of those small but distinct steps to enhance our performance and bring us somewhat closer to the ideal goal.

The following book therefore represents the first comprehensive guide, which aims to introduce this new modality to neurosurgeons, describing the currently available data, its clinical application, and future potential of this new technique.

Munich, Germany Bernhard Meyer, M.D.

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Abbreviations

2D	Two-dimensional
3D	Three-dimensional
ADC	Apparent diffusion coefficient
ADM	Abductor digiti minimi
AH	Abductor hallucis muscle
aMT	Active motor threshold
APB	Abductor pollicis brevis muscle
ARAT	Action Research Arm Test
aSTG	Anterior superior temporal gyrus
AVM	Arteriovenous malformations
BA	Brodmann area
BEM	Boundary element method
BIC	Biceps muscle
BMRC	British Medical Research Council
BOLD	Blood-oxygen-level-dependent
CCD	Coil-to-cortex distance
CI	Confidence interval
CNS	Central nervous system
COG	Center of gravity
CPS	Cortical parcellation system
CRS-R	Coma Recovery Scale-Revised
CSE	Corticospinal excitability
CSP	Cortical silent period
CST	Corticospinal tract
CT	Computerized tomography
cTBS	Contralesional theta-burst stimulation
DBS	Deep brain stimulation
DEC	Directionally encoded colors
DES	Direct electrical stimulation
dHb	Deoxyhemoglobin
DICOM	Digital imaging and communications in medicine
DLPFC	Dorsolateral prefrontal cortex
DOC	Disorder of consciousness
DT	Display time

DTI	Diffusion tensor imaging
DTI FT	Diffusion tensor imaging fiber tracking
DWI	Diffusion-weighted imaging
ECD	Equivalent current dipole
ECMS	Previous MCS
ECoG	Electrocorticography
ECR	Extensor carpi radialis muscle
EEG	Electroencephalography
e-field	Electric field
EMG	Electromyography
En-TMS	Electric field-navigated TMS
EOR	Extent of resection
EPSP	Excitatory postsynaptic potential
ER	Error rates
ERP	Event-related potentials
F1	Superior frontal gyrus (=SFG)
F2	Middle frontal gyrus (=MFG)
F3	Inferior frontal gyrus (=IFG)
FA	Fractional anisotropy
FACT	Fiber assignment by continuous tracking
FAT	Fractional anisotropy threshold
FCD	Focal cortical dysplasia
FCR	Flexor carpi radialis muscle
FDA	US Food and Drug Administration
FDI	First dorsal interosseus muscle
FEM	Finite element method
fMRI	Functional magnetic resonance imaging
FT	Fiber tracking
fT	Femtotesla
GC	Gastrocnemius muscle
GCP	Good clinical practice
GTR	Gross total resection
HDR	Hemispheric dominance ratio
HF	High frequency
HGG	High-grade glioma
HIS	Hospital information system
IAP	Intracarotid amobarbital procedure (=Wada test)
IC	Internal capsule
ICMS	Intracortical microstimulation
IEEE	Institute of Electrical and Electronics Engineers
IFC	Inferior frontal cortex
IFCN	International Federation of Clinical Neurophysiology
IFG	Inferior frontal gyrus
iFS	Inferior frontal sulcus
IOM	Intraoperative monitoring

IPI	Interpicture interval
IPSP	Inhibitory postsynaptic potential
ISI	Interstimulus interval
iTBS	Ipsilesional theta-burst stimulation
LF	Low frequency
LGG	Low-grade glioma
LIS	Locked-in syndrome
Ln-TMS	Line-navigated TMS
LTD	Long-term depression
LTP	Long-term potentiation
M1	Primary motor cortex
M2	Secondary motor cortex
MCS	Minimally conscious state
MEG	Magnetoencephalography
MEN	Mentalis muscle
MEP	Motor evoked potential
MFG	Middle frontal gyrus
MFL	Minimum fiber length
MPR	Multiplanar reconstruction
MRI	Magnetic resonance imaging
NBS	Navigated brain stimulation
NIBS	Noninvasive brain stimulation
NPV	Negative predictive value
NREM	Non-rapid eye movement
nrTMS	Navigated repetitive transcranial magnetic stimulation
nTMS	Navigated transcranial magnetic stimulation
OrO	Orbicularis oris muscle
OT	Occupational therapy
PACS	Picture archiving and communication system
PAS	Paired associative stimulation
PCI	Perturbational complexity index
PD	Parkinson's disease
PET	Positron-emission tomography
PMC	Premotor cortex
PMd	Dorsal premotor cortex
PNS	Peripheral nerve stimulation
PPC	Posterior parietal cortex
PPFM	*Pli de passage fronto-pariétal moyen*
PPV	Positive predictive value
PT	Phosphene threshold
PTI	Picture-to-trigger interval
RC	Recruitment curve
REM	Rapid eye movement
RMS	Root-mean-square
rMT	Resting motor threshold

ROI	Region of interest
rTMS	Repetitive transcranial magnetic stimulation (non-navigated)
S1	Primary somatosensory cortex
SAM	Synthetic aperture magnetometry
SD	Standard deviation
SEM	Standard error of mean
SFG	Superior frontal gyrus
sFS	Superior frontal sulcus
SMA	Supplementary motor areas
SMG	Supramarginal gyrus
SPECT	Single photon emission computed tomography
SQUID	Superconducting quantum interference device
STDP	Spike-timing-dependent plasticity
STG	Superior temporal gyrus
STR	Subtotal resection
TA	Tibialis anterior muscle
tACS	Transcranial alternating current stimulation
TBS	Theta-burst stimulation
TCI	Transcallosal inhibition
tDCS	Transcranial direct cortical stimulation
TES	Transcranial electrical stimulation
TMS	Transcranial magnetic stimulation (non-navigated)
TPJ	Temporoparietal junction
VAS	Visual analog scale
VNS	Vagus nerve stimulator
vPrG	Ventral precentral gyrus
VS	Vegetative state

Part I

General Aspects of nTMS

Basic Principles of Navigated TMS

1

Henri Hannula and Risto J. Ilmoniemi

1.1 Introduction

Neurons in the human brain can be triggered to fire action potentials by TMS (Barker et al. 1985; Ilmoniemi et al. 1999): a strong, quickly changing magnetic field is generated by a coil outside the head to induce, according to Faraday's law, an electric field (E-field) within the brain. The method is noninvasive: no contact to the patient is needed; no electric current is fed through the scalp or skull. The strong magnetic field itself has no direct biological consequences; the effect is entirely due to the E-field-driven electric current, which accumulates charge at conductivity boundaries such as cell membranes, depolarizing or hyperpolarizing them. Sufficient depolarization initiates synchronous action potentials that propagate in the axons just like naturally occurring ones; both anterograde and retrograde propagation is possible. The physiological consequences of TMS are mainly the result of action potentials triggered by sodium-channel opening, although, e.g., dendritic calcium channels might be activated by TMS as well.

At first, TMS was produced with nonfocal round coils, but soon the E-field-focusing figure-of-eight coil was introduced (Ueno et al. 1988). However, positioning of the coil was and still is often performed based merely on external landmarks on the head or by trial and error, meaning that the anatomical target in the cortex remains inaccurately known. This limitation was eventually eliminated by the

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introduction of navigated TMS, the so-called nTMS (see Ruohonen and Karhu 2010; Karhu et al. 2014), also called navigated brain stimulation (NBS; introduced by Nexstim Ltd. in 2003) or stereotactic magnetic stimulation (Krings et al. 2001). Navigated targeting based on magnetic resonance imaging (MRI) was originally proposed by Ilmoniemi and Grandori in the context of multi-coil stimulation (e.g., Ilmoniemi and Grandori 1996).

Initially, TMS navigation was performed simply by placing a figure-of-eight coil over the target area on the basis of the subject's individual MR image. The maximal activation was assumed to be located on the line that passes through the center of the coil perpendicularly to the surface of the coil bottom; this methodology is called "line navigation." However, it was realized (Fig. 1.1) and later confirmed that line navigation can result in inaccurate targeting if the coil is not perfectly tangential with respect to the skull (Sollmann et al. 2016).

Subsequently developed "E-field navigation," on the other hand, takes the geometry of the head into account, resulting in sufficient targeting accuracy for the most demanding clinical applications like presurgical mapping of eloquent cortex (Picht et al. 2011). In addition to the precise definition of the stimulator parameters such as coil shape, location, and orientation, individual head size and shape as well as the orientation of cortical folds have to be taken into account in order to know which sulcus or gyrus is stimulated. This is particularly important in clinical applications, where the location and dose of stimulation should be accurately defined.

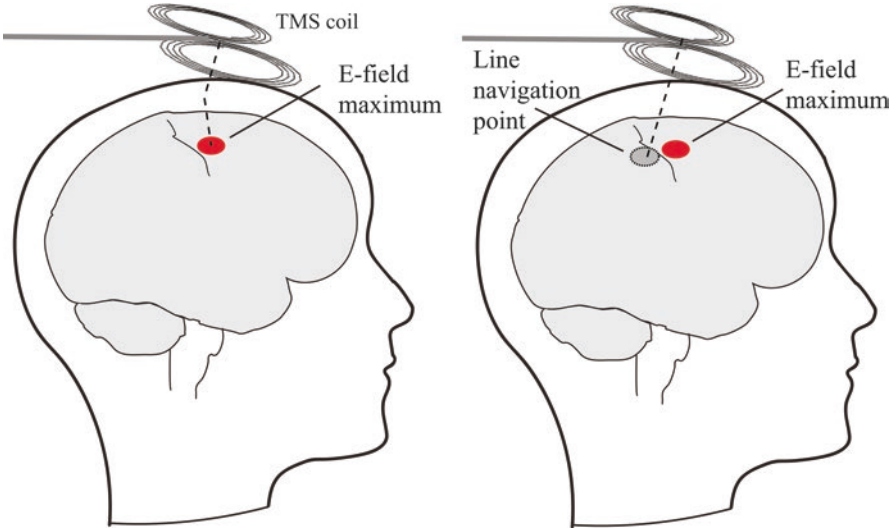

Fig. 1.1 The difference between line and electric-field (E-field) navigation. Somewhat analogously to light bending (refraction) at water–air boundaries, the electromagnetic influence of nTMS depends on air–tissue, skull–intracranial, and other conductivity boundaries. *Left*: E-field navigation takes into account the conductivity boundaries and computes the E-field maximum where the cortex is best stimulated. *Right*: Line navigation does not visualize the spot of maximal stimulation if there is any coil tilt

This chapter will provide an introduction to the basic physical, physiological, and technical principles of nTMS.

1.2 Basic Principles of TMS

The TMS pulse is generated by feeding a strong electric current to a coil placed over the stimulated cortical area. Figure 1.2 shows basic stimulator electronics: a capacitor, a charging circuit, and an electric switch that connects the capacitor to the coil. First, the switch is in the nonconducting state and the capacitor is charged to a voltage V_c of typically several kV. Then, the switch is closed, and the capacitively stored energy, $E_c = \frac{1}{2} C V_c^2$ is transformed to the energy of the magnetic field B: $E_B = \frac{1}{2} \mu_0 \int B^2 dV = \frac{1}{2} LI^2$, where μ_0 is the permeability of free space, L is the inductance of the TMS coil, and I is the coil current. The capacitor C and the inductance L form a resonant circuit with time constant $\tau = \sqrt{LC}$, resulting in a sinusoidal current waveform with frequency $f = (2\pi\tau)^{-1}$.

In biphasic operation (Fig. 1.2, upper row), one oscillatory cycle is completed if the switch is opened at the end of the cycle.

The lower row of Fig. 1.2 shows a circuit very similar to that of the upper row, but a diode has been added. This essentially prevents oppositely directed current, producing monophasic stimulation.

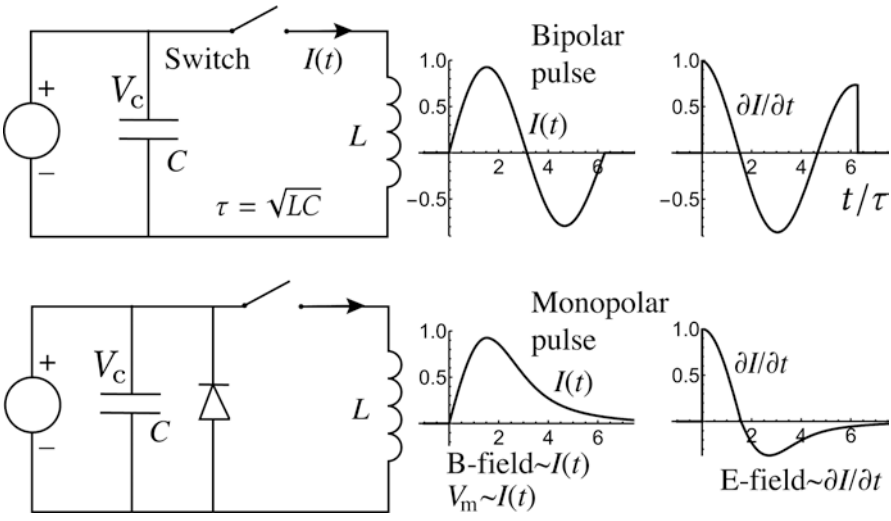

Fig. 1.2 Basic TMS circuits and corresponding waveforms. The E-field in the brain is proportional to the rate of change of the magnetic field while the change in membrane potential V_m, being proportional to the time integral of the induced current, is proportional to the magnetic field (B-field). However, for slow pulses, leakage currents through the cellular membrane and current flow within the cell reduce the change in membrane voltage relative to faster pulses with the same peak magnetic field. *Upper row*: bipolar circuit. *Lower row*: monopolar circuit

The spatial pattern of the magnetic field is defined by the shape and size of the coil. Two coil types are common: round coil and the so-called figure-of-eight coil. When the coil is placed over the scalp, the electric field induced in the brain is a blurred mirror image of the coil current (Koponen et al. 2015), the E-field strength being proportional to the time derivative of the magnetic field (Fig. 1.2). The round coil produces an unfocused annulus of current while the figure-of-eight coil produces a focal electric field. In the latter case, the electric fields of the two wings are additive under the center of the coil, doubling the electric field there. As shown quantitatively by Deng et al. (2013), small coils produce more focal and more superficial electric fields in the brain than large similarly shaped ones.

The TMS-induced intracranial current causes transient membrane potential changes, which, if these changes are sufficiently depolarizing, trigger action potentials. The induced electric field of a figure-of-eight coil being focal, a small target patch of cortex (of the order of 0.2–2 cm^2) can be selectively activated. It should be noted, however, that the focality depends on the TMS intensity: the stronger the pulse, the larger the area of cortex that is influenced (Fig. 1.3).

The effect of TMS is manifested in multiple ways. (1) The direct effect is triggering action potentials in cortical excitatory and inhibitory neurons. (2) Pyramidal cells send their signals to connected brain areas and to the spinal cord; the spread of the activity can be observed with electroencephalography (EEG; see Chap. 15; Ilmoniemi et al. 1997; Massimini et al. 2005; Ilmoniemi and Kicic 2010), fMRI (Fox et al. 1997), near infrared spectroscopy (Näsi et al. 2011), or, if the motor

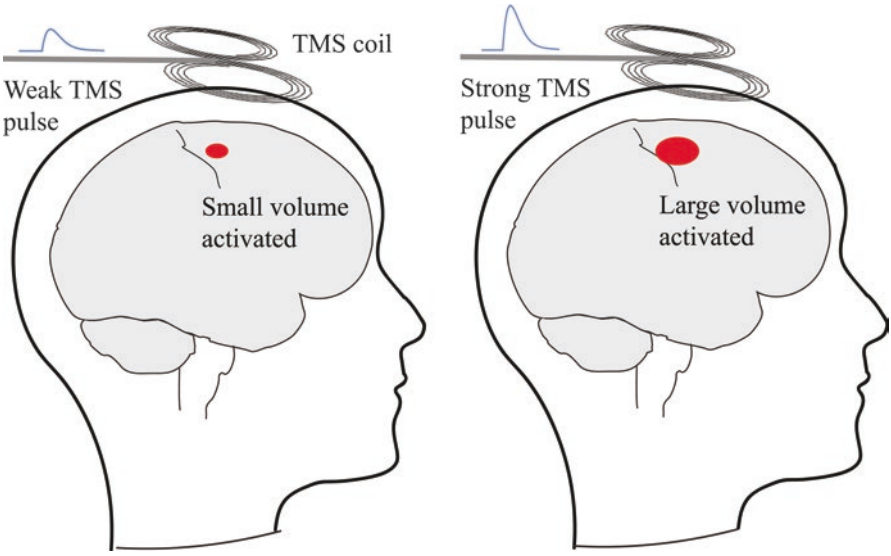

Fig. 1.3 Pulse intensity and stimulated volume. If a weak pulse is given, only a small volume near the peak electric field is activated. However, for strong pulses, the threshold of activation is exceeded in a large volume. Thus, in addition to a focal coil, maximal focality also requires that the stimulation intensity only slightly exceeds the activation threshold

cortex is stimulated, with electromyography (EMG) in the form of MEPs from muscles (Rothwell et al. 1999). (3) The activated inhibitory cells quiet down the stimulated site, causing the so-called cortical silent period (CSP), which in the case of the motor cortex is visible as dampened EMG signal lasting about 100–150 ms after the MEP (Säisänen et al. 2008). (4) TMS may disturb the processing or transfer of information in the target area, producing a "transient lesion"; thus, stimulation of the somatosensory or language areas can degrade sensory perception (Hannula et al. 2005) or language functions (Picht et al. 2013), respectively. (5) High-frequency (HF, ~10 Hz or more) repetitive TMS (rTMS) can increase cortical excitability while low-frequency (LF, ~1 Hz or less) rTMS can reduce excitability; such changes can outlast the stimulation period. Repeated sessions of rTMS can have therapeutic effects (Lefaucheur et al. 2014). (6) TMS can modulate ongoing oscillatory activity, which, in turn, may influence effective connectivity at least transiently.

Thus, the basic principle of TMS is simple: action potentials in the target area are triggered by E-field-driven currents that depolarize cell membranes. Based on precise knowledge of the shape of the coil and its location and orientation with respect to the head and its internal structure, the E-field pulse can be directed accurately to the target area. Such targeting, when an anatomical image of the brain is used as the map, is called E-field-navigated TMS (En-TMS).

1.3 Principles of Navigated TMS

1.3.1 General Considerations

In En-TMS, the induced intracranial electric field or the location of the maximum electric field is determined online and is usually displayed on anatomical brain images in order to allow targeting the pulses to desired cortical structures. The accurate determination of the electric field requires knowledge of (1) the precise geometry of coil windings, (2) coil current as a function of time, (3) the location and orientation of the coil with respect to the head, (4) the size and shape of the head and its compartments, and if detailed analysis of the electric field within the brain is performed, (5) the conductivity values and profiles of different head compartments such as cerebrospinal fluid, gray matter, and white matter. Since the magnetic field penetrates tissues without distortion and since virtually no current is fed to the brain through the scalp or skull, the conductivity values of the scalp and skull do not play a big role in determining the induced current flow in the brain. This is in stark contrast to transcranial electrical stimulation (TES) where these conductivity values as well as the details of skull thickness and shape play a crucial role.

Focal En-TMS is comparable to DES of the brain in that it produces a stimulating electric field that is confined to a small area of tissue. The benefit of En-TMS over DES is of course its noninvasiveness that allows one to perform presurgical mapping without risks or time pressure and therapeutic stimulation in populations where invasive procedures cannot be considered. Although En-TMS is administered transcranially, the lack of distortion of the magnetic field by intervening tissues has

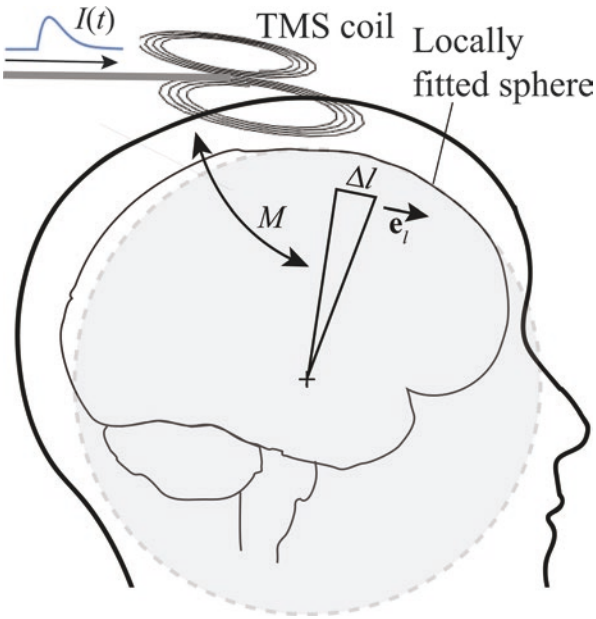

Fig. 1.4 Computing the TMS-induced electric field. The triangle construction can be used to compute the TMS-induced electric field. The E-field component in the direction $\boldsymbol{e}_l$ at the short edge of the (imagined) triangle is $E_l = dI/dt\, M/\Delta l$, where M is the mutual inductance between the TMS coil and the triangle, $I(t)$ is the current fed into the TMS coil, and Δl is the length of the short edge of the triangle. The vertex opposite to the short edge is at the center of the sphere that is fitted to the local radius of head curvature near the location of the coil or the short edge

allowed it to be developed to a level of accuracy that is at par with DES in clinical applications (Takahashi et al. 2013).

The three-dimensional (3D) structure of the head is often approximated with the so-called spherical model, in which the conductivity is assumed to be spherically symmetric, i.e., being only a function of the distance from the center of the sphere. In areas of the head where the local curvature is approximately spherical, this approximation has been shown to provide quite accurate results both in practice (Picht et al. 2011) and in simulations (Nummenmaa et al. 2013). However, the spherical model is accurate only if the sphere is fitted to the local curvature of the head, not the whole head (Fig. 1.4). This is precisely what is done by the En-TMS systems designed for the demanding clinical work such as presurgical localization of eloquent cortex.

It is particularly straightforward to calculate the TMS-induced electric fields inside a spherically symmetric conductor. Consider a triangular path within a (locally) spherically symmetric conductor as in Fig. 1.4, where one of the vertices is at the center of symmetry. At the short edge of the triangle, the E-field component $\boldsymbol{E}_l$ in the short-edge direction, $\boldsymbol{e}_l = \boldsymbol{\Delta l}/\Delta l$, is

$$\boldsymbol{E}_l(t) = \boldsymbol{E}(t) \cdot \boldsymbol{e}_l = M\left(dI(t)/dt\right)/\Delta l,$$

where M is the mutual inductance between the triangular path and the TMS coil, Δl is the length of the short edge of the triangle, and $I(t)$ is the current fed into the coil. Easily programmable formulae for mutual inductances have been presented by Grover (1946).

It may be worth mentioning another relationship (Ilmoniemi et al. 1996) that can be used to compute E-field values, not only in the case of the spherical model but also in the general case. This relationship ties TMS to what is common knowledge in MEG. Namely, the electric field $\mathbf{E}(\mathbf{r}')$ at location $\mathbf{r}'$ induced by TMS coil current I is proportional to the "lead field" $\mathbf{L}$ of the coil.

$$\mathbf{E}(\mathbf{r}') = dI / dt\,\mathbf{L}(\mathbf{r}').$$

In MEG, the lead field expresses the sensitivity of a pickup coil to primary or source currents $\mathbf{J}^{\mathrm{p}}$ in the brain so that the flux Φ threading the pickup coil is a weighted integral of the source currents:

$$\Phi = \int \mathbf{J}^{\mathrm{p}}(\mathbf{r}') \cdot \mathbf{L}(\mathbf{r}')\,\mathrm{d}\mathbf{r}'.$$

If a head model (spherical, realistically shaped, or more detailed realistic model) and a solution to the forward problem are available, i.e., if one can calculate $\Phi(\mathbf{Q}, \mathbf{r}')$ threading the coil due to current dipole $\mathbf{Q}$ at location $\mathbf{r}'$, then $\mathbf{L}(\mathbf{r}')\cdot\mathbf{Q} = \Phi(\mathbf{Q}, \mathbf{r}')$. The Cartesian components of the lead field at $\mathbf{r}'$, $\mathrm{L}_x(\mathbf{r}')$, $\mathrm{L}_y(\mathbf{r}')$, and $\mathrm{L}_z(\mathbf{r}')$ can thus be calculated by computing $\Phi(\mathbf{e}_x, \mathbf{r}')$, $\Phi(\mathbf{y}_x, \mathbf{r}')$, and $\Phi(\mathbf{e}_z, \mathbf{r}')$, respectively.

As pointed out above, the local sphere model in En-TMS is sufficiently accurate for state-of-the-art presurgical localization of motor and language areas. However, the accuracy can be further improved if more realistic models of the head are available. The boundary element method (BEM; Nummenmaa et al. 2013) can be used if the head conductivity structure is approximated by compartments of uniform conductivity. Often, 3- or 4-compartment models are used in these calculations, but even a single-layer model (intracranial space with uniform conductivity) is quite accurate because current flow within the skull, which has poor electrical conductivity, has a very limited effect on the induced currents in the intracranial space. For the 3-compartment model, head MRI is segmented to intracranial, scalp, and skull volumes. In the 4-compartment model, the intracranial cavity is further divided into two parts: the cerebrospinal fluid and the brain. A limiting factor of BEM in practical real-time En-TMS has been the computational load, but this limitation is already subsiding with better algorithms and faster computers.

In principle, even more accurate modeling can be achieved with the finite element method (FEM), in which the conductivity is described at the level of small voxels, each of which can be assigned an individual conductivity value; these values can even be anisotropic (Opitz et al. 2011). Unfortunately, FEM suffers from several practical issues. First, the computation time is far too long for real-time navigation. Second, with typical voxel sizes of 3–5 mm, conductivity boundaries and conductivity gradients become very poorly represented, and the results from FEM can be less accurate than those from BEM.

A practical, real-time solution to En-TMS was developed by Nexstim Ltd. (Helsinki, Finland). Keeping track of the stimulator parameters and the coil's location, orientation, and tilting, the system calculates the electric field using the local sphere model fitted to the individual head shape in a region below the coil. This local sphere approach is also called multiple-sphere approach. Local-sphere modeling has turned out to be highly successful and is now approved for clinical use (US Food and Drug Administration = FDA Predicate 510(k) number for the Nexstim NBS system K091457 for motor mapping and K112881 for the combination of the Nexstim NBS system used with NexSpeech® for language mapping).

1.3.2 How Does nTMS Work?

The technique of nTMS was developed to make targeting based on individual MRI (the navigation map) possible and visible. For the accurate navigation needed in diagnostics or in modulation of brain activity in targeted therapy, one has to eliminate uncertainty in the technical (nonphysiological) factors that affect the stimulation level at the neurons. For both, nTMS accuracy and visibility, the physical parameters of the coil (location, orientation, tilt, size, and shape of the copper windings) and the stimulator pulse waveform and amplitude need to be accurately determined and taken into account.

In addition to the technical TMS parameters, we need physical parameters of the individual head and brain for the calculation of the stimulating intracortical electric fields; structural information for this purpose can be obtained from MRI. The MRI scan needs to include the whole head so that the nose, ears, and head surface are all visible and thus accessible as landmarks. Typically, T1-weighted, 3D MRI scans with 1 × 1 × 1-mm voxels are used, as they are also required for intraoperative neuronavigation. With the MRI, individual brain morphology with patient-specific structural forms such as cortical convolutions becomes visible and thus applicable for nTMS targeting.

Navigation tools needed to locate the TMS coil and to align the MRI scan with the patient's head include the head and coil trackers and the digitizer pen; these are located in real time with a 3D position sensor (Figs. 1.5 and 1.6).

The head tracker, acting as a reference tool, is used to locate the head and to monitor its movements. The coil tracker can then indicate the coil's location and 3D orientation in relation to the head, i.e., in the head coordinate system. The digitizer pen is used to determine arbitrary location coordinates, e.g., to align the MRI scan and the head by pointing at landmarks that are visible both in the MRI and on the head. After the registration of the MRI and the individual head coordinate systems (aligning the MRI and the real head), the stimulating electric field in the brain can be calculated from the knowledge of coil and stimulation parameters and visualized in real time on the MRI (Ruohonen and Ilmoniemi 2005).

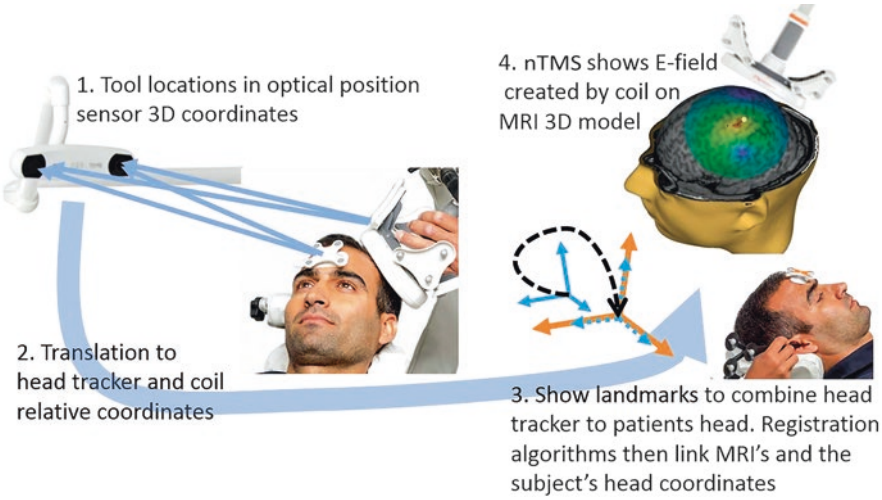

Fig. 1.5 3D navigation. The principle of En-TMS with online calculation and targeting based on the electric field (E-field). The stimulation session is started with registration to align the MRIs to the individual head. After successful registration, the stimulating E-field is displayed online over the 3D MRI brain topology to guide stimulation targeting when the coil is moved

1.3.3 Contributors to Accuracy

Being critical for many clinical applications, the accuracy of nTMS targeting has raised many questions and discussions as long as this technique has been available. Although it is crucial for operators to understand the determinants of spatial accuracy of nTMS, there is very limited literature or published data on this topic. Some of the publications report nTMS precision (variability or repeatability) instead of accuracy; this can lead to misinterpretations. It is therefore important to clarify the meaning of these terms. The US FDA (FDA 1995) gives a clear definition of accuracy by referring to the Institute of Electrical and Electronics Engineers (IEEE) standards: "The measure of an instrument's capability to approach a true or absolute value" and "A quantitative measure of the magnitude of error." Precision is a quite different measure: "The relative degree of repeatability, i.e., how closely the values within a series of replicate measurements agree."

Based on the FDA definition, nTMS accuracy is a measure of the typical distances from the visualized stimulation point to the real *in vivo* location of the maximal electric field. This targeting error is of course a random variable and usually unknown; a useful way to describe this error is its standard deviation. In a good En-TMS system, the standard deviation of the error may be 5–6 mm, comparable to that in determining eloquent cortical areas during surgery by DES.

The navigation system displays the location of the electric field maximum on the individual MRI of the cortex. The accuracy of determining the visualized electric field depends on how accurately the multiple parameters and variables used in the

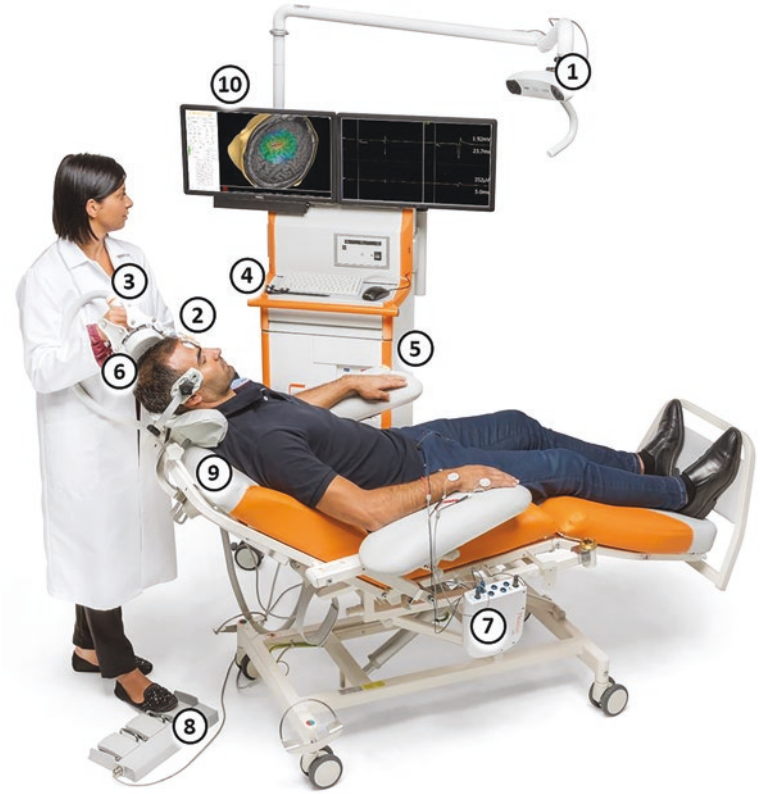

Fig. 1.6 E-field-navigated TMS hardware. (1) Positioning sensor (optical)—tracking the tools; (2) Head tracker—location and movement of the head; (3) Coil tracker—location, orientation, tilting of the coil; (4) Digitizer pen—enables recording of individual points, e.g., for MRI registration; (5) TMS stimulator—producing the controlled pulse adjusted by the navigation software; (6) Coil—producing the TMS pulse, output controlled by the navigation software; (7) EMG—response measurement for MEPs, synchronized to each stimulus and enabling the coloring of the stimulation spot based on the MEP amplitude; (8) Foot pedal—to apply stimulus when the electric field is targeted at the right spot; (9) Chair with head rest—good ergonomics for operator and subject; (10) nTMS system display for controls and targeting the stimulating electric field

calculations are known: intensity of stimulus, stimulator parameters, coil shape and location, orientation and tilting of the coil, head shape, size, and electrical conductivities. The position sensor used for tracking the navigation tools must have a high spatial accuracy. Indeed, a typical error for a modern optical position sensor is only 0.2 mm, but this is only a minimal part of the total error for an nTMS system. Unfortunately, in some of the published nTMS literature, the accuracy of optical position sensor is reported instead of the overall accuracy. Also sometimes only the precision with which a previous nTMS coil location can be determined is mentioned; precision is typically much better than accuracy, since many of the errors are

constant across the repeated stimulations like inaccuracies in MRI, uncertainties in the conductivity model, or errors in tracker calibration. To properly characterize the En-TMS accuracy, it should be divided to groups (here, a–d) that independently impact the reliability of the determination of the visualized stimulation spot location:

(a) Determination of coil location and 3D orientation
- Manufacturing tolerances for the coil and coil trackers, digitizer pen, and head tracker
- 3D localization of the reference (head) tracker and the coil by optical (or electromagnetic) techniques

(b) Computational model of the stimulating electric field
- Fitting of the conductor model to head-shape information
- Modeling the stimulation coil (shape, size, details of the copper windings)
- Head conductor model (sphere, multiple-compartment model)
- Computational method (Spherical-model formulas, BEM, FEM)

(c) Errors in alignment of MRI scan to individual head
- Registration algorithm that aligns the individual MRI and the real head
- Operator errors in alignment procedures, when pointing of head landmarks with the digitizer pen
- MRI resolution and quality
- MRI susceptibility distortions

(d) Movement of the reference (head) tracker during examinations
- Head-tracker movement (reference tool) during the stimulation session, affecting the calculated coil position and the E-field pattern

If the system is built from individually designed stand-alone components, including a TMS stimulator with a coil not initially designed to be navigated, navigation software, position sensor with trackers to be installed to the coil, and an EMG device, all connected together as an nTMS system, the overall accuracy can be determined only by testing the particular combination. In addition to this, there exist nTMS systems that operate without E-field navigation. For the integrated En-TMS system that calculates the stimulating electric field, the accuracy can be derived from independent uncertainties by the square root of the sum of squared errors. Table 1.1 gives an example on how the accuracy of one En-TMS system (Nexstim Plc., previously Nexstim Ltd.) has been calculated; this system was clinically validated for the localization and assessment of the motor cortex and motor tract integrity for preoperative planning. The specifications of other manufacturers' equivalent accuracy specifications are not published or accessible yet.

To integrate En-TMS into clinical workflow, dedicated En-TMS protocols are developed to ensure consistent targeting accuracy. The multiple factors affecting the

Table 1.1 Error sources

Error source	Mean error in E-field stimulation spot (mm)
Coil localization: • Manufacturing tolerances for the coil and coil trackers • 3D localization with optical position sensor	1.6
Head tracker movement (reference tool) during the stimulation session	3.1
Computation of the stimulating electric field: • The output and characteristics of stimulation coil • Model of the intracranial electric field • Fitting of the model to the individual head	3.8
Registration to MRIs: • MRI image imperfections • Registration algorithms	2.5
System accuracy with root square sum of all error sources: $\sqrt{(1.6)^2+(3.1)^2+(3.8)^2+(2.5)^2}$	5.7

Error sources contributing to the accuracy of an En-TMS system (in this example: Nexstim eXimia NBS)

results include the definition of individualized stimulation intensity, E-field direction, and response detection. The nTMS workshop group 2016 has recently finalized a summary of their protocol meeting, describing the motor mapping protocol that has been demonstrated to work in presurgical planning. Section 1.4 of this chapter includes a summary of the protocol's key factors; it also lists an nTMS system's general software and hardware features that are essential for the clinical use of En-TMS.

1.3.4 E-field Navigation vs. Line Navigation

Currently, there are two basic nTMS principles. En-TMS is a technique where the stimulating electric field is calculated and navigated at the cortex, while in the so-called line navigation, the stimulation spot is assumed to be on the line that passes through the geometric center of the coil and is perpendicular to the coil surface. Line-navigated TMS (Ln-TMS) is prone to increased errors when the coil is not held continuously tangentially against the head. In practice, there is a continuous need to adjust coil tilting when moving the coil along the head surface. The effect of the head in En-TMS versus Ln-TMS can be seen in primary motor cortex (M1) hand area stimulation of a healthy subject (Figs. 1.7 and 1.8).

As highlighted in Figs. 1.7 and 1.8, E-field navigation and line navigation may indicate the stimulation spot in different gyri depending on local head curvature and coil tilting. There is very limited literature where these two methods have been compared. A recently published study by Sollmann et al. (2016) was designed to compare stimulus targeting in tumor patients with an En-TMS system and an

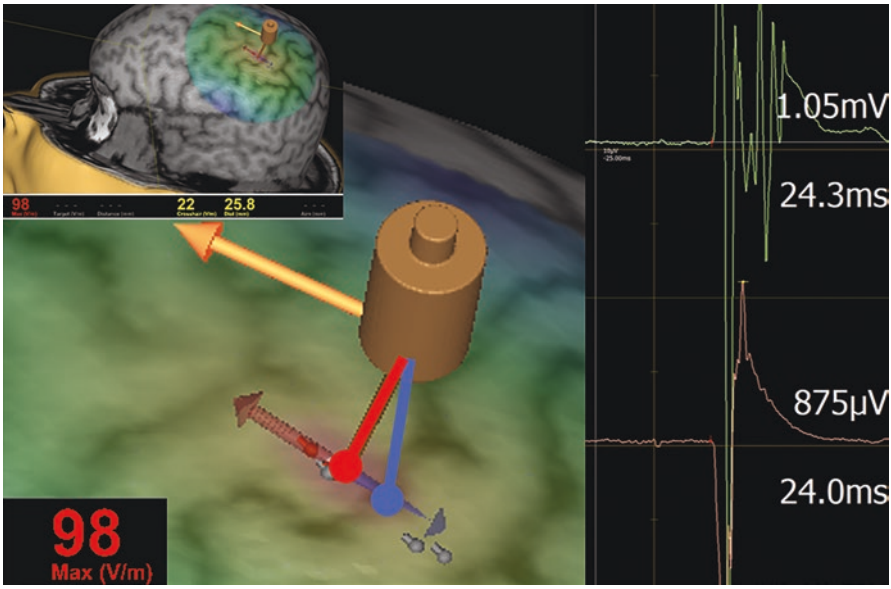

Fig. 1.7 M1 stimulation with E-field navigation. *Right*: EMG view from the nTMS software: the *top green line* indicates a MEP from the abductor pollicis brevis (APB) with 24.3-ms latency and 1.05-mV amplitude; the *bottom purple line* shows a MEP from abductor digiti minimi (ADM) with 24.0-ms latency and 875-µV amplitude. *Left*: 3D stimulation targeting view from the nTMS: view from E-field-targeted stimulation of M1. The *red line* and *dot* indicate the maximum of the electric field in M1. The electric field in this hotspot, 98 V/m, caused the 1.05-mV MEP; the E-field orientation was perpendicular to the sulcus at the APB representation area. The *blue line* and *dot* visualize line navigation, which points misleadingly to the primary sensory cortex (S1), which has no motor function to produce the MEPs from APB or ADM. This was demonstrated with the E-field-targeted S1 stimulation visible in Fig. 1.8

Ln-TMS system. In this clinical study, only the data generated by the clinically validated FDA-approved En-TMS system could be used for tumor-patient diagnostics (Picht et al. 2011, 2014; Forster et al. 2011; Krieg et al. 2012, 2013; Tarapore et al. 2012). However, the clinical team compared motor mapping with a broadly distributed Ln-TMS system also marketed for preoperative motor mapping in 12 patients suffering from brain tumors in order to examine potential differences in clinical applicability, workflow, and mapping results between the two navigation techniques.

The nTMS-naïve operator who had no previous nTMS experience was trained for both devices by the manufacturers. Motor mappings were performed with both nTMS systems on each patient in an alternating pattern starting with either En-TMS or Ln-TMS. Study outcomes comparing En-TMS and Ln-TMS were as follows:

1. The upper- and lower-extremity motor maps generated by En-TMS and Ln-TMS were different, resulting in only partial overlap of the results.

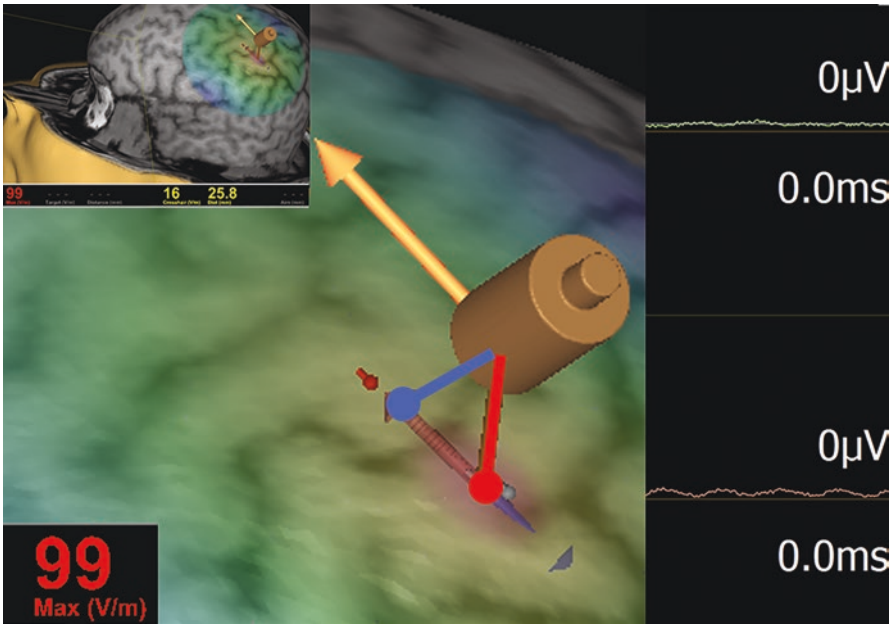

Fig. 1.8 S1 stimulation with E-field navigation. *Right*: EMG view from the nTMS software: the *top green line* indicates the absence of MEP from APB and the *bottom purple line* the absence of MEP from ADM. *Left*: 3D stimulation targeting view: The *red line* and *dot* indicate the maximum of the electric field in S1 (postcentral gyrus). Here, the electric field of 99 V/m causes no MEP. The *blue line* and *dot* point to assumed stimulation location in M1 according to line navigation. Line navigation is misleading in this case due to the fact that no MEP (amplitude 0 μV) is coming from the APB or ADM muscles

2. In two patients, Ln-TMS and En-TMS identified the motor hotspot in different gyri. It is important to note that these are initial data for the comparison due to the fact that only 6 out of 12 patients' ipsilateral mappings and 8 out of 12 contralateral mappings could be completed due to technical hardware problems in the Ln-TMS device (these problems were unrelated to the stimulation targeting method).
3. Distances between En-TMS and Ln-TMS motor hotspots were 8.3 ± 4.4 mm on the ipsilesional and 8.6 ± 4.5 mm on the contralesional hemisphere.
4. The number of those (motor-positive) spots where nTMS succeeded to elicit MEPs was significantly higher for En-TMS (En-TMS vs. Ln-TMS, 128.3 ± 35.0 vs. 41.3 ± 26.8, $p < 0.0001$).
5. The ratio of motor-positive spots and the number of stimulations was higher for En-TMS: En-TMS vs. Ln-TMS, 38.0 ± 9.2% vs. 20.0 ± 14.4%, $p = 0.0031$.
6. Both technical approaches are quick to learn and fast in operation, allowing mapping large areas of cortex in a given time. The learning process for En-TMS and Ln-TMS was studied by comparing overall mapping durations and speed for the first and last mapping conducted: In En-TMS, the time per stimulation was

reduced by 75.9%, while the number of stimulations per mapping was increased by 66.5%. In Ln-TMS, a reduction of time per stimulation was only 29.0%, and the number of stimulations per mapping was decreased by 9.1% meaning that the necessity of manual placing of the coil on the head tangentially makes the mapping itself more time-consuming despite learning effects.

According to the authors, the above-mentioned significantly higher ratio of positive responses could be seen favorable toward En-TMS regarding more elaborate capabilities to optimize coil location, tilting, and orientation during the stimulation, since coil orientation has been reported to be one of the key factors for optimized stimulation (Ruohonen and Karhu 2010; Schmidt et al. 2015). En-TMS is able to calculate and visualize the electric field online with its orientation and dose, allowing the continuous optimization of coil positioning. The authors stated that Ln-TMS shows the location of the coil without providing information about coil angulation with respect to the subject's head. The way the Ln-TMS indicates the coil's orientation with the line projection may lead to nonoptimal coil orientation and tilting with decreased electric field at the cortex; this could explain the lower rate of overall stimulations that led to a positive response.

Conclusions from this first En-TMS and Ln-TMS motor mapping comparison in neurosurgical context: *Although both nTMS systems tested in the present study are explicitly designed for application during motor mapping in patients with brain lesions, there are differences in applicability, workflow, and results between En-TMS and Ln-TMS, which should be distinctly considered during clinical use of the technique. However, to draw final conclusions about accuracy, confirmation of motor-positive Ln-TMS spots by intraoperative stimulation is crucial within the scope of upcoming investigations. As already done for En-TMS, future studies using intraoperative DES have to examine whether Ln-TMS is also able to detect valid and sufficiently accurate motor maps in the neurosurgical context.*

1.3.5 Clinical Validation of Accuracy

The accuracy in clinical practice of En-TMS systems has been evaluated in brain tumor patients only with the Nexstim system so far. Data on Ln-TMS mapping are currently awaited.

A meta-analysis of Takahashi et al. (2013) reviewed articles where the En-TMS system was used to map patients with Rolandic brain tumors. They reported: "The mean distance between motor cortex identified on nTMS and DES by using the mean distance in 81 patients described in six quantitatively evaluated studies was 6.18 mm" (Takahashi et al. 2013). The review article also concludes that nTMS "is the only modality that is analogous to DES in that it allows for electrical stimulation of the brain and observation of the induced effect" due to the fact that the nTMS "technique spatially correlates well with the gold standard of DES." Chapter 5 outlines the details of the different studies analyzed in this meta-analysis.

Since the FDA motor mapping approval of En-TMS in December 2009, 54 original neurosurgical articles for preprocedural planning with 2350 patients have been published. These include five presurgical motor-mapping articles, with 633 patients reporting the impact of nTMS motor maps on better clinical outcomes. This data base is not yet available for Ln-TMS, but first clinical studies are expected.

1.4 Practical Issues and Examples of the Use of NTMS

1.4.1 General Consideration

TMS is based on the fact that a changing magnetic field induces an electric field to cause neuronal activation or transient alterations of neuronal excitability in order to diagnose or modify brain functions. E-field-guided navigation was developed to rule out uncertainties and to improve repeatability. Diagnostics of the motor cortex can be done by single-pulse TMS to probe corticospinal excitability (CSE). However, CSE measurements have variability due to physical and physiological factors (Danner et al. 2008). An integrated En-TMS system controls, guides, and records physical parameters of TMS like coil tilting, orientation, location, and stimulator output and estimates the stimulating electric field at the individual brain anatomy. A system setup with an integrated EMG has enabled investigations in which these parameters are partitioned with stepwise regression to find out the variance of physical parameters in CSE measurement (Schmidt et al. 2015). This study also indicated the validity of calculated and visualized electric fields with the model used by an En-TMS system. Results of the study highlight that:

- CSE variability is reduced when the physical parameters can be controlled with the help of navigation.
- The calculated and visualized electric field of the En-TMS system is valid.
- The spatial accuracy of En-TMS is better than 5 mm.
- Small fluctuations of physical parameters can influence statistical comparisons of CSE measurements.

1.4.2 Factor: E-field Location

Schmidt et al. (2015) conclude that in their En-TMS study, the spatial definition of En-TMS is possibly as small as 2 mm. Location changes larger than 2 mm resulted in significantly increased CSE variability, meaning that CSE measurements are much more susceptible to small changes in physical parameters than might be expected from previous studies.

1.4.3 Factor: Orientation of the Stimulating Electric Field

The orientation of the electric field has a clear impact on TMS responses (Schmidt et al. 2009; Kallioniemi et al. 2015). The importance of the optimal orientation

perpendicular to the gyrus is reported in En-TMS and DES comparison studies (Krieg et al. 2012; Picht et al. 2009, 2011; Tarapore et al. 2012), suggesting that suprathreshold nTMS mapping may lead to combined activation of transsynaptic pathways and direct stimulation of axonal pathways deeper in the gray matter and in the bends of white matter axons (Amassian et al. 1992). Action potentials are created when large enough membrane depolarization is caused by the TMS-induced electric field. TMS is most effective when the stimulating electric field is oriented longitudinally and orthodromically with respect to the largest population of neurons at the stimulation target, which in most stimulation spots means the direction perpendicular to the gyrus. This is why the orientation of the coil has to be confirmed before individual resting motor threshold (rMT) definition. The rMT is required to find the optimal mapping intensity by repeated stimulation of the optimal hotspot location while turning the coil in 20° steps in both directions as long as responses are seen. When doing motor mapping close to a lesion or when obtaining motor responses far away from the assumed primary motor cortex, it is important to repeat the stimulations with E-field orientation changed by +45° and −45° to test the population of the neurons at the stimulation target and to confirm consistency of the motor responses.

1.4.4 Factor: rMT-Guided Stimulation Intensity

To create focal stimulation for high-resolution mappings, the stimulation intensity must be defined individually by determining the rMT and by adjusting the stimulation intensity to 110% rMT to get responses every time when a motor-relevant area is targeted. It is important to realize that stimulator output in % of the maximum output from the capacitor does not tell much about the stimulation intensity at the cortex due to the impact of coil distance from the cortex, coil tilting, coil location, and coil orientation. While nTMS motor mapping with 110% rMT is regarded standard, some teams find the mapping result even more focal when using 105% rMT as stimulation intensity. If weaker pulses are given, e.g., 105% rMT, a smaller volume of neurons near the peak electric field is activated. However, the use of too low intensity harbors a severe risk to miss some functional areas during the mapping. Moreover, all validation studies were performed using a stimulation intensity of 110% rMT. In contrast, in the case of strong pulses, e.g., 130% rMT, the threshold of activation is exceeded in a large volume, thus leading to more unspecific maps. For accurate rMT definition, the hotspot and optimal orientation must be determined before running the rMT algorithm. Suboptimal definition of the hotspot and E-field orientation may lead to higher mapping intensities due to an erroneously high rMT value, compromising the resolution of mapping due to activation of larger neuronal volumes. Thus, in addition to a focal coil, a pulse only slightly above activation threshold can be used for good focality.

1.4.5 Factor: E-field Strength and Location

Schmidt et al. (2014) stimulated the primary motor cortex of healthy subjects, providing evidence for the importance and validity of En-TMS motor mapping.

The key factor here is that the navigation system knows and controls the electronics and hardware for the stimulation delivery and response measurement. Schmidt et al. (2014) demonstrated that changes in E-field strength and location result in associated changes in MEP amplitudes, showing MEP susceptibility to small changes of E-field values calculated and visualized at the brain. Coil tilting and distance from the individual anatomy among the other parameters mentioned before affect the electric field. When moving the coil during the mapping session, it is important to follow the E-field values, location, and orientation.

1.4.6 Factor: Preactivation

Continuous triggered EMG monitoring of target muscles during the motor mapping is essential. Preinnervation in the target muscle is known to strongly modify the MEP amplitudes; in the Schmidt et al. (2014) study, more than tenfold effects were observed. To keep the mapping session stable, the preinnervation needs to be minimized by keeping the patient comfortable and thus the muscles relaxed. Temporary tension of the target muscle between the relaxations during the mapping helps to minimize preinnervation during stimulation.

1.4.7 Factor: Anatomy

To map the individual brain, the morphology, with its unique shapes, structures, and cortical convolutions of each person, needs to be taken into account. The orientation of the electric field must be defined and tested individually according to anatomical structures. A standardized coil orientation with respect to external landmarks of the skull is not sufficient for preoperative mapping of eloquent cortical areas or for delivery of therapeutic stimulation. The mapping also needs to exceed the area of interest, especially when individual patterns of sulci and gyri cannot be determined by any morphometric landmarks. In presurgical planning, the anatomical structures are often smeared by tumor growth, edema, bleeding, and/or vascular alterations. The orientation of the electric field needs to be changed again by +45° and −45° in these locations in order to check for the consistency of the motor responses.

1.5 Current Motor Mapping Protocol

The above-mentioned factors of accuracy are crucial for precise use of nTMS, especially En-TMS. In order to put these abstract technical data into a clinical context, this section explains the different steps of nTMS motor mapping by using the protocol of the nTMS workshop group 2016 and by referring to the factors outlined in section 1.4.

1.5.1 Preparation of the Session

1. Upload the patient's MRI to the system; based on the individual MRI, the software generates a 3D head model.
2. Prepare the patient (interview, checking for contraindications (Chap. 4), explaining the procedure, attaching EMG leads).
3. Align the patient's head with the MRI-based 3D head: (1) Attach the head tracker to the patient's forehead as reference tool for tracking by the infrared camera; the head tracker will allow free head movement by the patient; (2) point with the digitizer pen at the 3 points predefined as MRI landmarks (left ear crus of helix, nasion, right ear crus of helix); (3) touch with the pen 9 points around the head, guided by the software. Typical tool-tracking accuracy is better than 1.5 mm (mean); the head as a whole can be aligned with the MRI at 2-mm accuracy when the software-guided registration process with 3 + 9 points is followed.

1.5.2 Hotspot Identification

1. Identify the hand knob at 20–25-mm depth from the scalp, and adjust the stimulator output to 80–100 V/m.
2. Adjust the stimulation intensity to be suitable for mapping (muscle at rest, MEP latencies 15–25 ms).
   (a) If MEP amplitudes are >500 μV, lower the intensity 1–2% of the stimulator output.
   (b) If MEP amplitudes are <100 μV, increase the intensity until APB MEP amplitude is 100–500 μV.
3. Rough mapping (Fig. 1.9): Stimulate along the central sulcus toward the midline and toward the Sylvian fissure, keeping the E-field orientation perpendicular to the central sulcus, until no more MEPs are evoked. Select the largest APB response and set the corresponding location as the stimulation target.
4. Test the coil orientation: Check the EMG amplitude in this 0° orientation. Repeat stimulations on the marker with the aiming tool (Fig. 1.10, right panel), while turning the coil 20° in both directions after each stimulus. Check the amplitude (μV) after each stimulus. Select the coil orientation evoking the largest MEP for defining the rMT.

The En-TMS software provides an aiming tool that allows the operator to stimulate only if the location is within 2 mm and coil orientation and tilting within 2° of those of the target position to ensure that rMT determination is performed with the coil at the predetermined location and orientation (Fig. 1.10). The stimulation of the same anatomical location with the coil in different orientations is allowed by the system when the location control is not activated to ensure that rMT determination is performed with the coil orientation producing the largest responses.

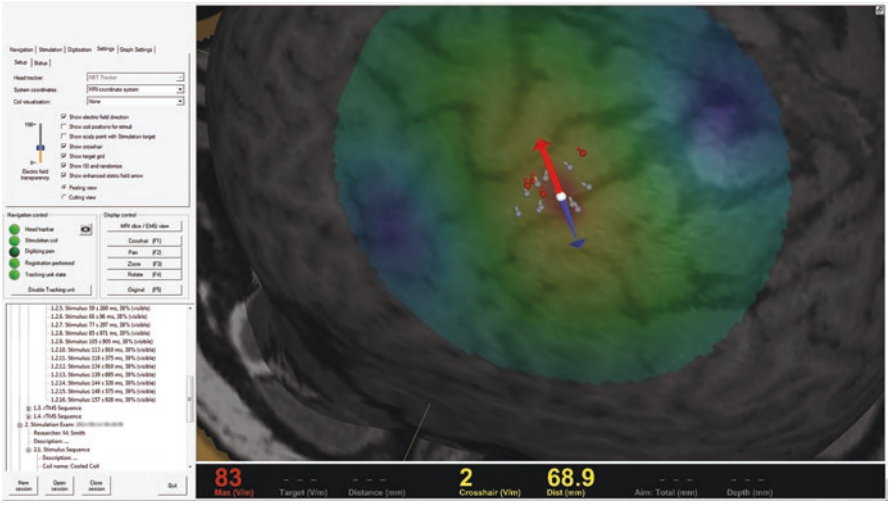

Fig. 1.9 Hotspot identification. *Colors* correspond to motor response in each location: *White*: MEP ≥1 mV peak-to-peak amplitude; *Red*: MEP = 50–500 μV; *Gray*: MEP ≤50 μV (no response). The direction of the stimulating electric field is highlighted with the *red* and *blue arrows*. The stronger stimulation direction is displayed as a *red arrow* and the weaker stimulation direction as a *blue arrow*. The *arrows* start at the stimulation hotspot. The En-TMS software calculates the electric field at the chosen target location based on a validated head model, which utilizes a predefined set of over 40,000 locally fitted spheres; the coil design and manufacturing specifications enable focal and precise delivery of TMS pulses that generate E-field patterns that corresponds to the one calculated by the software; the recording and display of the TMS-evoked EMG responses is synchronized with stimulus delivery, providing instant feedback; the software guides the user to place the nTMS coil in the right place and orientation in relation to brain anatomy to focus the electric field at the target and to enable electric field to be perpendicular to the stimulated sulcus

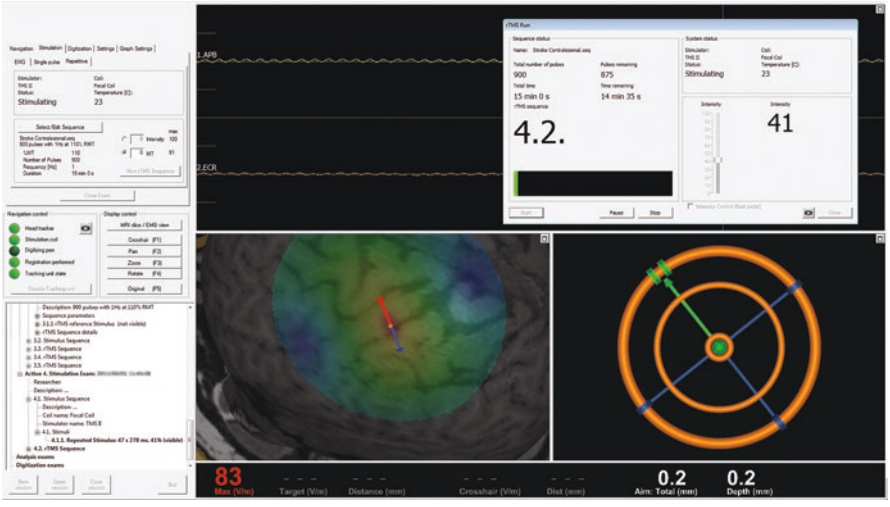

Fig. 1.10 Visualizing E-field orientation with En-TMS. *Left lower corner*: View showing the location of the E-field maximum and E-field orientation at the maximum. *Right lower corner*: The aiming tool that helps to reproduce stimulations with identical coil location and 3D orientation

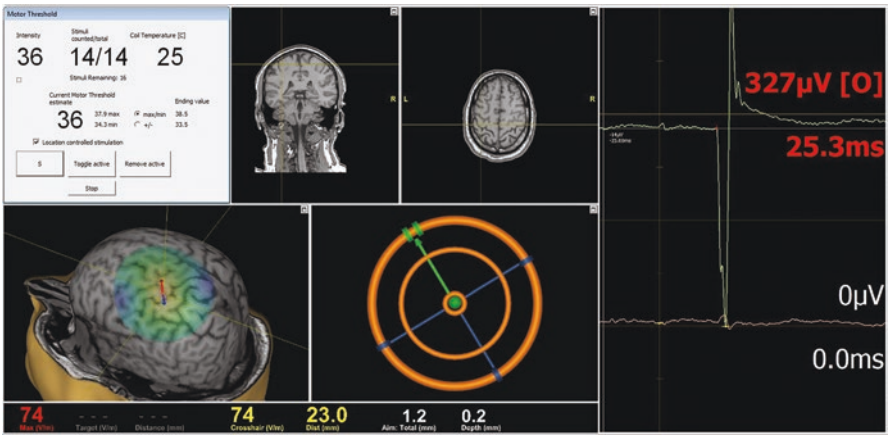

Fig. 1.11 EMG response. Integrated online EMG monitoring and response control for each stimulus enables computer-aided rMT determination. After each stimulus, the peak-to-peak amplitude of the muscle response is checked and the software classifies the response as "over" or "under" the amplitude threshold (character "O" or "U"). Responses with non-physiological latency or amplitude as well as those with preceding muscle tension are rejected. After each stimulus, the algorithm shows and adjusts the stimulator output for the next stimulus. The rMT determination is finished when the error bounds of the rMT estimate fall below the set value or when the number of stimuli reaches a pre-specified maximum

1.5.3 rMT Determination

1. Select the optimal stimulation from Sect. 1.5.2 step 4 as reference stimulation to be repeated with exactly the same coil location, tilting, and orientation with the help of the targeting tool (Fig. 1.11 bottom middle window).
2. Start the rMT determination software by selecting the target muscle EMG channel and setting the ending parameters: Integrated online EMG monitoring and response control for each stimulus enables computer-aided rMT determination for automated control of mapping intensity (see Fig. 1.11 for details).
3. Verify the rMT by repeating the stimulation with the suggested value ten times. If fewer than five responses out of ten stimuli, elicit a proper response, increase the intensity by 1%, and start over again. If you get ten responses out of ten stimuli, decrease the stimulation intensity by 1% and start over again.

1.5.4 Mapping of Hand Motor Area with 110% rMT

1. Set the stimulator output to 110% of the rMT defined previously (optional: refined mapping at 105% rMT).

   Stimulate along the central sulcus, precentral gyrus, postcentral sulcus, and precentral sulcus with 2–3-mm spacing while keeping the E-field orientation perpendicular to the local sulcus (Fig. 1.12). Expand the mapping area as long as motor responses are detected. There should be a rim of one or two rows surrounding the MEP-positive area, in which nTMS was not able to elicit MEPs. When obtaining motor responses far away from the assumed primary motor

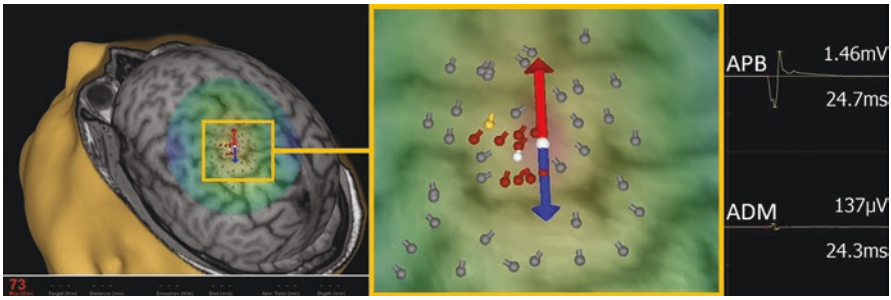

Fig. 1.12 E-field orientation for hand area mapping. This *screenshot* shows a hand area mapping with 110% rMT, with APB and ADM as target muscles. The stimulating E-field orientation is to be maintained perpendicular to the central sulcus. The direction of the electric field is indicated in each stimulus location with a small sphere and a cylinder. The cylinder direction is the same as the *red arrow* during targeting (*middle view*). *Colors* correspond to motor response strength as in Fig. 1.9

cortex or close to the lesion (e.g., tumor), repeat stimulation with +45° and −45° in these locations to test the consistency of the motor responses.

2. Verify registration integrity after mapping. The nTMS system enables 3D visualization of the digitizer pen with the 3D MRI after the 12-point MRI-to-head registration. The operator can take at any time of the session the digitizer pen and move it over the scalp to check from the nTMS display that the tip of the pen moves correspondingly over the scalp in the 3D head view. A separate digitization exam enables digitization of extra scalp landmarks that can be seen in the 3D head view and checked at any time on the system 3D view by pointing at landmarks with the digitizer pen. If the pen is not shown correctly on the head, the operator must redo the 12-point MRI-to-head registration.

1.5.5 Mapping of Leg Motor Area (TA, Soleus)

1. Preferentially, the tibialis anterior (TA) or abductor hallucis muscle representation area near the junction of the central sulcus and longitudinal fissure is stimulated first with 110% rMT +20 V/m intensity. Leg muscles should be kept initially at rest. Keep the E-field orientation perpendicular to the longitudinal fissure, the electric field pointing laterally.
2. If motor responses are obtained, continue stimulation by following the longitudinal fissure 2 cm anteriorly and 2 cm posteriorly. Stimulate also perpendicular to the medial parts of central sulcus, up to 3 cm from the longitudinal fissure as far as responses emerge.
3. If no responses are obtained, use the following procedure as outlined in Figs. 1.13 and 1.14.
4. Verify the registration after mapping. Move the digitizer pen over the scalp to check from the nTMS display that the tip of the pen moves correspondingly over the scalp and touches the scalp landmarks in the 3D head view.

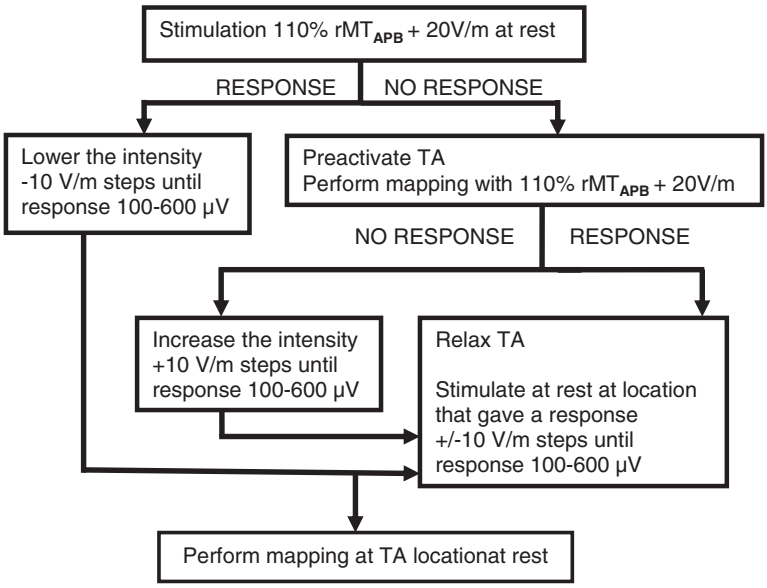

Fig. 1.13 Algorithm for lower extremity mapping. The chart describes the different steps of lower extremity mapping

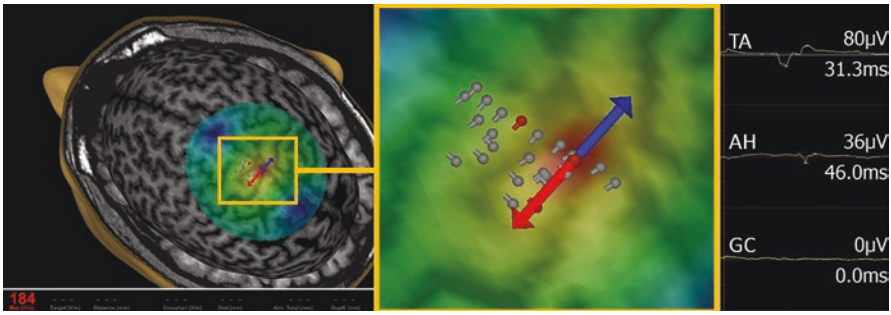

Fig. 1.14 E-field orientation for lower extremity mapping. This screenshot shows a leg area mapping of three target muscles: TA, abductor hallucis (AH), and gastrocnemius muscle (GC). The stimulation is done with an E-field orientation perpendicular to the longitudinal fissure with the electric field oriented laterally at the junction of the central sulcus and the longitudinal fissure. *Colors* as described in Fig. 1.9

1.5.6 Mapping of Facial Muscles (Mentalis, Orbicularis Oris)

1. Facial representation area in the lateral parts of the central sulcus in the precentral gyrus is stimulated first with 110% rMT +20 V/m stimulation intensity (or perform an rMT determination for the face area separately). Facial muscles should be kept initially at rest. Keep the coil orientation first perpendicular to central sulcus.

2. If motor responses are obtained, continue stimulation by following the longitudinal fissure 2 cm anteriorly and 2 cm posteriorly as far as responses emerge.
3. If no responses are obtained, use the following procedure as outlined in Figs. 1.15 and 1.16.
4. Verify the registration after mapping.

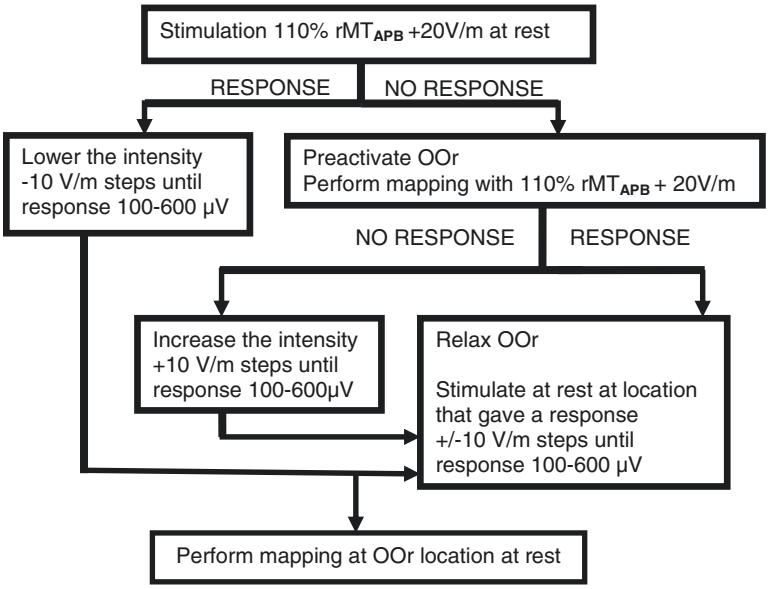

Fig. 1.15 Algorithm for face mapping. The chart describes the different steps of face mapping

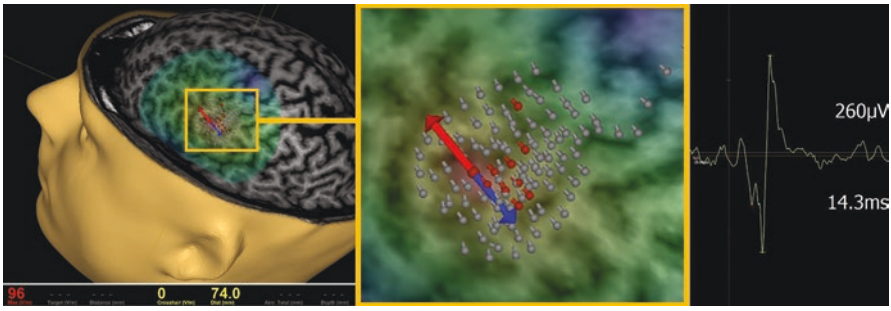

Fig. 1.16 E-field orientation for face area mapping. This *screenshot* shows a face area mapping of the orbicularis oris muscle (OrO). The stimulation should be done with E-field orientation perpendicular to the central sulcus. Colors as in Fig. 1.9

1.6 Conclusion

A strong, quickly changing magnetic field generated by a coil outside the head induces, according to Faraday's law, a stimulating electric field within the brain. The navigation of the stimulating electric field was developed to solve many of the issues associated with nTMS accuracy, reliability, reproducibility, and usability. In the clinically validated En-TMS system, the accurate targeting of the stimulating electric field is enabled by the focal figure-of-eight coil design, reproducible stimulator pulse delivery, and individual MRIs with accurate head alignment and integrated controlled response measurements via triggered EMG. Such system design minimizes the influence of nonphysiological factors on the accuracy of nTMS so that clinical application for preoperative motor and language mapping became feasible.

By addressing all the factors influencing accuracy as outlined in this chapter, the En-TMS technology with individual E-field modeling can now provide the level of accuracy, reliability, and reproducibility sufficient for neurosurgical applications.

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nTMS, MEG, and fMRI: Comparing and Contrasting Three Functional Mapping Techniques

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2.1 Introduction

Neuroimaging is a cornerstone of modern practice in the fields of neurology, neuro-oncology, and neurosurgery. Techniques such as computerized tomography (CT) and MRI have revolutionized the clinician's ability to diagnose, treat, and follow patients with neoplastic processes of the CNS. The last 2 decades have seen the introduction of additional techniques that go beyond simple anatomic and structural description, offering insights into the function of CNS structures themselves. These functional neuroimaging techniques enable clinicians to characterize a neoplastic lesion not just in an anatomical context but also in the context of the overall neurological function of the patient, thus reducing treatment-related morbidity. Should a lesion require surgical management, intraoperative imaging techniques have enhanced the neurosurgeon's ability to maximize EOR without compromising neurological function. Finally, in the following patients, long-term, serial functional imaging plays an integral role in defining the evolution of the functional relationship between an identified neoplastic lesion and its surrounding structures. In short, the significant improvements in morbidity and mortality associated with neoplastic lesions of the CNS are due in large part to the advancement of neuroimaging techniques.

This chapter briefly summarizes the available functional imaging techniques that are in common clinical use. For most of these modalities, a detailed discussion of underlying physics is beyond the scope of the text; however, details will be provided if they are

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directly relevant to understanding the clinical application. The techniques of nTMS, MEG, and fMRI will be covered, as well as the strengths and weaknesses of each. Finally, the reasons for selecting each study in clinical practice will be discussed.

2.2 Functional Imaging Techniques

Functional imaging is being utilized increasingly in the characterization of intracranial lesions, particularly in the preoperative setting to evaluate eloquent brain regions in patients with brain tumors. It is most useful in the management of lesions within or near eloquent cortex such as motor or visual cortex because, by defining the function of perilesional parenchyma, it allows for optimization of surgical strategy by, for example, identifying the safest route of access for a deep-seated lesion. It also allows clinicians to discuss the morbidity associated with a given lesion in specific and accurate terms, thereby giving patients clearer understanding of the ramifications of various management strategies (e.g., observation vs. subtotal resection vs. aggressive resection). Functional imaging is therefore an invaluable modality for identifying the clinical sequelae associated with a given lesion.

2.3 Functional MRI

2.3.1 General Principle

The technique of fMRI uses MRI to measure changes in the BOLD signal, which is a reflection of the changing ratios of oxyhemoglobin and deoxyhemoglobin in functionally active brain regions. Because functionally active brain has a higher energy requirement than resting brain, the metabolic activity within functional brain is increased. This increased metabolic demand results in greater oxygen consumption, thereby altering the ratio of oxyhemoglobin to deoxyhemoglobin within the tissue.

Since its advent in 1991, fMRI has become the dominant modality for functional brain imaging in both the clinical and the research community for a number of reasons. It is safe, involves no ionizing radiation, and is completely painless for the subject. It allows for whole-brain coverage, including the ability to examine activity in deep brain structures. Importantly, the widespread availability of commercial and open-source tools for analysis of fMRI data has enabled many researchers to embrace this technology easily. Finally, the acquisition of MRI data in standard formats allows for seamless integration of fMRI datasets with existing workstations of the picture archiving and communication system (PACS) and intraoperative frameless stereotactic navigational systems.

2.3.2 Clinical Application

In the clinical setting, particularly in patients with brain tumors, fMRI has been used to identify sensorimotor cortex (Fig. 2.1), as well as language and visual cortices (DeYoe and Raut 2014; Hirsch et al. 2000; Kapsalakis et al. 2012; Gupta 2014).

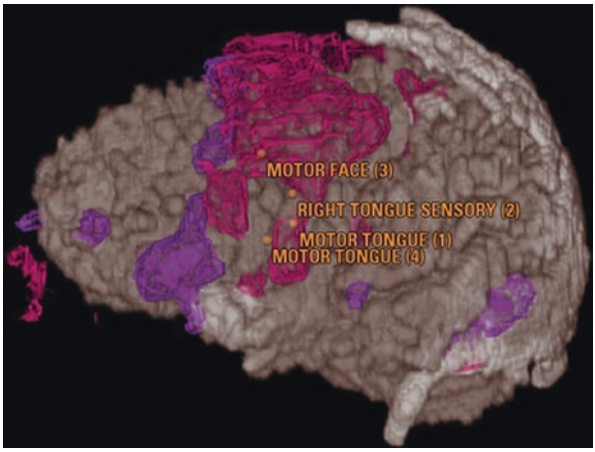

Fig. 2.1 fMRI vs. DES mapping. fMRI of motor (*pink*) and premotor areas (*purple*). Intraoperative DES mapping results (*orange dots*) are overlaid on the 3D volume. The motor region (*pink*) defined by fMRI is more extensive than that defined by DES mapping; this lack of specificity makes fMRI suboptimal as a stand-alone technique for the identification of eloquent cortical regions

Currently, the use of fMRI to delineate regions associated with specific language tasks (i.e., word repetition, word reading, and object naming) is in the experimental stage. Similarly, language lateralization with fMRI is a subject of significant continuing research and is rapidly reaching equivalent sensitivity and specificity to Wada testing, but has not achieved a sensitivity or specificity sufficient to become the gold standard for language lateralization (Abou-Khalil 2007).

2.3.3 Limitations

The fMRI principle is limited by the fact that the BOLD signal is an indirect measure of neural activity. In effect, the BOLD signal is three steps removed from the process it is meant to quantify: oxyhemoglobin/deoxyhemoglobin ratio is a proxy for oxygen demand, which is a proxy for metabolic activity, which is a proxy for neuronal activity, which is a proxy for function. Moreover, because it is limited by the rate of oxygen consumption and subsequent blood flow mechanism, fMRI lacks the temporal resolution required to image the dynamic and oscillatory spatiotemporal patterns that are associated with cognitive processes. Furthermore, it might not accurately reflect true neuronal processes, especially in regions of altered vasculature, as frequently occuring in patients with neurosurgical pathology that are undergoing fMRI for the purpose of mapping eloquent cortices. In fact, the exact frequency band of neuronal processes that corresponds to the BOLD signal is still being actively debated (Logothetis et al. 2002; Niessing et al. 2005). Finally, in the context of speech and language studies, because fMRI measurements involve loud scans caused by fast forces on MR gradient coils, the scans themselves invoke auditory responses that have to be deconvolved from the signals in order to examine other stimulus-related activity. Hence, to image brain activity noninvasively on a

neurophysiologically relevant timescale and to observe neurophysiological processes more directly, silent imaging techniques that have high temporal and spatial resolution are needed.

2.4 Magnetoencephalography

2.4.1 General Principle

MEG measures tiny magnetic fields outside of the head that are generated by neural activity. Because it measures these fields directly, in contrast to fMRI, MEG offers excellent temporal resolution (<1 ms). Furthermore, magnetic fields are unimpeded by biological tissue, so MEG recordings offer an undistorted signature of underlying neural activity.

Biomagnetic fields detected by MEG are extremely small, in the tens to hundreds of femto-Tesla (fT) range—seven orders of magnitude smaller than the Earth's magnetic field. As a result, appropriate data collection necessitates a magnetically shielded room and highly sensitive detectors called superconducting quantum interference devices (SQUIDs) (Vrba and Robinson 2002). The fortuitous anatomical arrangement of cortical pyramidal cells allows the noninvasive detection of their activity by MEG. The long apical dendrites of these cells are arranged parallel to each other and often perpendicular to the cortical surface, and their electromagnetic fields sum up to magnitudes large enough to be detected at the scalp. Synchronously fluctuating dendritic currents result in electric and magnetic dipoles that produce these electromagnetic fields (Okada et al. 1987, 1999). These dendritic currents from the brain are typically sensed using detection coils called flux transformers or magnetometers, which are positioned closely to the scalp and connected to SQUIDs. SQUIDs act as magnetic-field-to-voltage converters, and their typically nonlinear response is linearized by flux-locked loop electronic circuits. SQUIDs have a sensitivity of ~10 fT per square root of Hz which is adequate for detection of the brain's magnetic fields (Vrba and Robinson 2001, 2002).

Modern MEG systems often consist of simultaneous recordings from many differential sensors that cover the whole head, with the total number of SQUIDs varying from 100 to 300. Typical MEG systems have sensors that are spaced approximately 2.2–3.6 cm apart. Although the maximum sampling rate is approximately 12 kHz, most MEG data is usually recorded at about 1 kHz, thereby maintaining excellent temporal resolution for measuring the dynamics of cortical neuronal activity at the millisecond level.

MEG scanners, however, are expensive and relatively rare, so MEG is less widespread than MRI-based techniques. MEG studies are useful for localization of sensory, motor (Nagarajan et al. 2008), and language regions (Fig. 2.2) (Edwards et al. 2010). They are also used to localize seizure foci, which is often helpful in the management of epileptogenic tumors such as oligodendrogliomas. Finally, a recently described MEG-based algorithm for language lateralization successfully identifies the language-dominant hemisphere with accuracy approaching that of Wada testing, the current gold standard (Findlay et al. 2012).

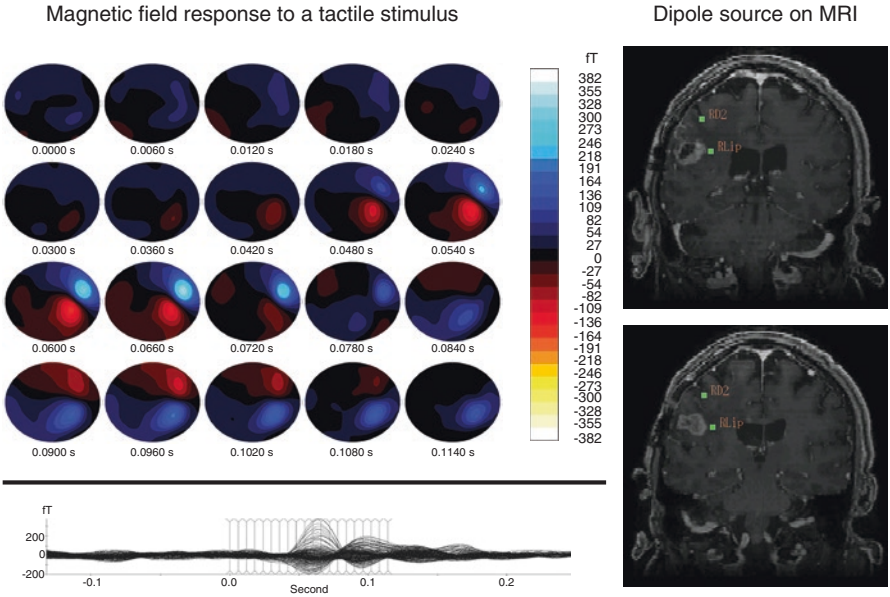

Fig. 2.2 MEG recordings of somatosensory stimuli. Sample MEG of somatosensory stimuli to the right lip (RLip) and right index finger (RD2). Multiple stimulus trials are performed for each site and cortical magnetic fields are recorded. The trials are averaged and a single dipole is reconstructed for each site using the least-square fit method. On the left are depicted the results in 0.006 s intervals, with the magnetic dipoles represented as *red-orange* (negative fT) to *blue-white* (positive fT). On the right, the resulting dipoles are then displayed on a coregistered, T1-weighted post-gadolinium coronal MR slice. On the bottom of the figure is the overall time course of magnetic field with all trials superimposed

MEG signals must be reconstructed using complex algorithms to quantify the underlying brain activity from observed sensor data. This reconstruction of brain activity from MEG data typically involves two major components—a forward model and an inverse model. The details of these algorithms are complex and beyond the scope of this chapter. Depending on the type of source reconstruction chosen, the quality of the signal data, and the particular characteristics of the machine itself, the spatial resolution of MEG can vary. As a rule of thumb, for typical datasets, newer beamforming methods can reconstruct tens to hundreds of sources at about 5 mm distances (assuming time-frequency separation and detectability). This estimate can be considered an approximate spatial resolution for MEG, keeping in mind that under certain circumstances the spatial resolution can be even greater.

2.4.2 Clinical Application

MEG can be an effective tool for functional mapping in patients undergoing preoperative workup for brain tumor surgery (Gallen et al. 1995; Kamada et al. 1993; Makela et al. 2001). This modality has been used for localization of the

sensorimotor cortex along the central sulcus (Gaetz et al. 2009; Korvenoja et al. 2006; Taniguchi et al. 2004; Ossenblok et al. 2003) as well as mapping the primary auditory (Rowley and Roberts 1995; Lutkenhoner et al. 2003) and visual cortices (Plomp et al. 2010).

The primary motor cortex and the sensory cortex are located on the anterior and posterior wall of the central sulcus, respectively. Identifying the hand region (Gaetz et al. 2009; Korvenoja et al. 2006; Schiffbauer et al. 2003; Ishibashi et al. 2001; Nagarajan et al. 2008) and the mouth region (Schiffbauer et al. 2003; Kirsch et al. 2007) of the primary sensorimotor cortex has been useful for presurgical evaluation and also confirmed with intracranial DES mapping.

Motor evoked fields can be recorded by time-locking the MEG signal corresponding to movement (Rezai et al. 1996) and single equivalent current dipole (ECD) fitting of the corresponding evoked field generated from the average sensor data (Kober et al. 2001; Kirsch et al. 2007; Schiffbauer et al. 2003; Ishibashi et al. 2001; Korvenoja et al. 2006). Using this approach, Schiffbauer et al. compared MEG to intraoperative mapping in tumor patients receiving painless tactile somatosensory stimulation to the lip, hand, and foot and found that both approaches had a favorable degree of quantitative correlation (Schiffbauer et al. 2003). Similarly, a favorable degree of quantitative correlation was also seen from utilizing dipole fitting with MEG versus fMRI (Kober et al. 2001). Confirmed with electrocorticography (ECoG), dipole fitting of evoked magnetic fields to median nerve stimulation proved to be superior to fMRI for 15 patients in identifying the sensorimotor cortex (Korvenoja et al. 2006). Following dipole fitting of the mouth motor cortex, DES sites were usually anterior and lateral to MEG localization of the lip somatosensory cortex (Kirsch et al. 2007).

The use of MEG spatial filtering holds promise for a more robust method for mapping the motor cortex in presurgical patients (Gaetz et al. 2009; Cheyne et al. 2006; Nagarajan et al. 2008). The use of a spatial filter beamformer while subjects performed a self-paced index finger movement can generate high-resolution imaging of the spatiotemporal patterns of premotor and motor cortex activity (Fig. 2.3) (Cheyne et al. 2006; Tarapore et al. 2012b). Peaks of the tomographic distribution of beta-band event-related desynchronization sources reliably localized the hand motor cortex in a group of 66 patients, which was confirmed with DES (Nagarajan et al. 2008).

Location of the language cortex (i.e., Broca's area and Wernicke's area) also holds clinical value as mass lesions can distort the anatomy and also because of interindividual anatomic variation among patients. Recently, Hirata et al. used synthetic aperture magnetometry (SAM, an improvement over MEG dipole methods) to prospectively determine language lateralization and found high concordance with Wada testing and intraoperative cortical stimulation results (Hirata et al. 2010). Extending this approach, SAM has been used to accurately characterize dynamics of language dominance using MEG (Findlay et al. 2012).

MEG has also been used to quantify functional connectivity in peritumoral regions, a technique that may have implications regarding the risk of postoperative complications. The term functional connectivity essentially defines the complex

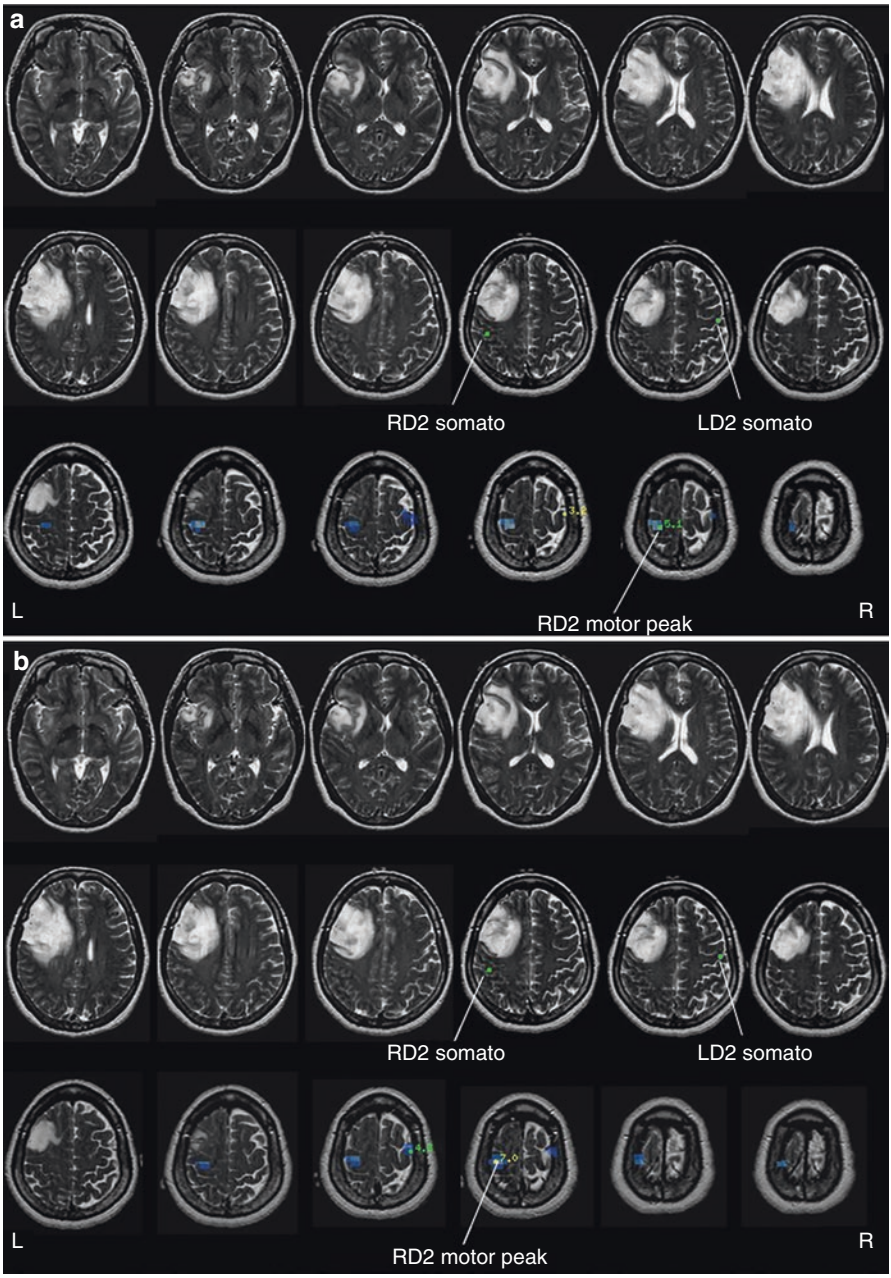

Fig. 2.3 MEG recordings of motor stimuli. (**a**) Localization of β-band desynchronization preceding right index finger flexion for a subject with a frontal tumor. The location of hand motor cortex relative to a single dipole localization of hand somatosensory cortex is also shown. (**b**) Localization of β-band desynchronization due to left index finger flexion in the same subject, showing contralateral hand motor cortical activation in the right hemisphere

functional interaction between local and more remote brain areas. When compared with healthy controls, all patients with brain tumors had diffuse brain areas with decreased alpha coherence, as well as a decrease in high frequency bands for long distance connections and an increase in slower frequency bands for more local connections (Bartolomei et al. 2006). Two follow-up studies have demonstrated that, by quantifying the functional connectivity in the peritumoral region, connectivity maps help to predict regions of positive intraoperative stimulation (Martino et al. 2011). Furthermore, these connectivity maps demonstrate that patients with high peritumoral connectivity are at greater risk of postoperative deficit than patients with low peritumoral connectivity (Tarapore et al. 2012a).

2.4.3 Limitations

In addition to being relatively rare, MEG can be limited by its relative preference for specifically oriented field sources: it senses primarily the tangential currents in the brain closer to the surface (Hamalainen 1991). In addition, the postprocessing requirements for MEG are substantial, both from the standpoint of the technical knowledge of complex signal processing algorithms and from the standpoint of raw computational power. MEG datasets are large, and processing them requires substantial resources, often distributed over a computer cluster involving several servers. Because of its high sensitivity, MEG can also be impeded by magnetic noise: occasionally, a few dental fillings will render a patient's scan unusable. As data acquisition and signal processing algorithms improve, MEG will contribute increasingly valuable functional imaging data in the clinical setting.

2.5 Navigated Transcranial Magnetic Stimulation

2.5.1 General Principle

Please see Chap. 1 for further technical details of the nTMS technique. In order to serve the overview character of this chapter, outlining each modality, this following paragraph provides a short summary on the technical background of nTMS.

The technique of nTMS has demonstrated great promise in functional mapping of the human cortex. Based on Faraday's principle of electromagnetic induction, TMS applies a brief pulse of high-strength magnetic field over the scalp which passes through the skull and induces an electrical current in the underlying brain region (Wagner et al. 2007). These pulses of current, if applied appropriately, are sufficient to depolarize a population of neurons, inducing an action potential (Mills et al. 1987). Single TMS pulses, when delivered over the cortex, will thus briefly stimulate the underlying cortical region. Repetitive trains of these pulses, so-called rTMS, can have either an inhibitory or a stimulatory effect on cortical excitability, depending on the frequency of the rTMS trains (Kobayashi and Pascual-Leone 2003). Therefore, by altering the protocol of stimulation, TMS can cause either a

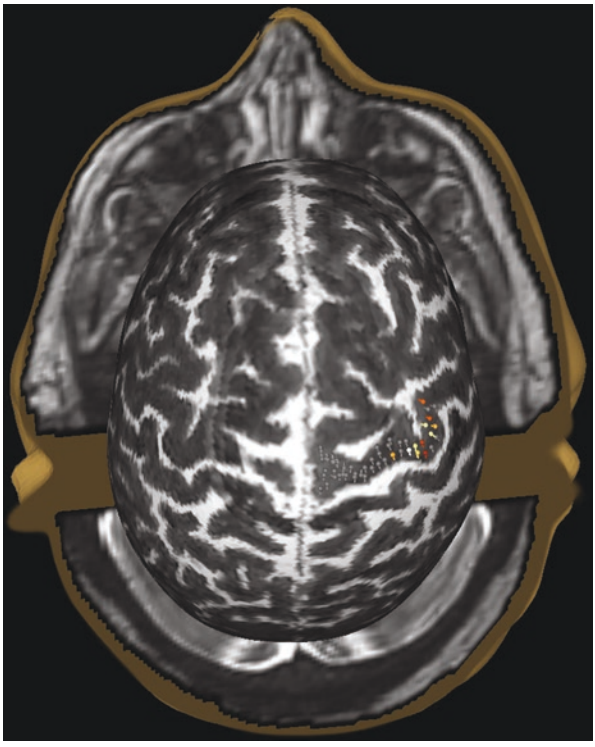

Fig. 2.4 nTMS motor map. A motor map of the precentral gyrus generated with nTMS. Variably colored pins indicate the amplitude of MEPs in APB during the mapping procedure (*white*, MEP ≥1 mV peak-to-peak amplitude; *red*, *orange*, *yellow*, MEP = 50–500 μV; *gray*, MEP ≤50 μV (no response))

temporary excitation or lesion effect in the cortex. The technique has been used for decades, although its application in neurosurgical patients has been more recent. Nevertheless, it has an excellent safety profile (Tarapore et al. 2016a, b) (please also see Chap. 4).

Furthermore, the development of nTMS has allowed for this technology to arrive rapidly at the forefront of noninvasive mapping modalities (Fig. 2.4). What sets apart the nTMS system from a nonnavigated TMS system is its demonstration, in real time, of the precise location and strength of the magnetic pulse. By integrating a frameless stereotactic navigational system (such as those used and commonly utilized in neurosurgical and other procedures) with an nTMS coil, one can coregister a structural MRI or CT brain scan to a subject's anatomy using fiducial markers or anatomical landmarks. This advancement allows the investigator to deliver TMS pulses with unprecedented precision under image guidance (Julkunen et al. 2009; Krings et al. 2001a, b; Picht et al. 2009). Furthermore, in some nTMS systems, the strength and directionality of each TMS pulse are calculated on the fly according to a dynamic spherical model which takes into account the preset parameters of

stimulation as well as the subject's scalp/skull thickness (Sarvas 1987; Tarkiainen et al. 2003). As a result, when the stimulation coil is positioned over the subject's scalp, the investigator can visualize the targeted cortical region, the strength and orientation of the magnetic dipole, and the cone of activation generated by the magnetic pulse.

The nTMS technique therefore allows the investigator, for the first time, to pinpoint precisely the cortical region that is being targeted. This capacity for accurate targeting offers the possibility of mapping essential cortical regions associated with motor and language function. Prior studies (Pascual-Leone et al. 1991; Michelucci et al. 1994; Jennum et al. 1994; Wassermann et al. 1999; Epstein et al. 1996, 1999, 2000) have examined the use of rTMS to cause speech arrest and lateralize language (see below for details). However, these efforts were not stereotactically guided and showed rTMS to be an unreliable technique for determining language laterality, largely because of a high false-positive rate for speech arrest sites on the supposedly nondominant hemisphere.

2.5.2 Clinical Application

The clinical application of nTMS is discussed in detail throughout this book and will not be summarized in detail in this chapter. Briefly, nTMS is commonly used in the management of peri-Rolandic tumors, where the pyramidal tract is at highest risk of disruption from surgical resection, and has shown to correlate well with intraoperative DES (Picht et al. 2011; Krieg et al. 2012; Tarapore et al. 2012b). Additionally, nTMS is used increasingly for preoperative language mapping in patients with neoplastic lesions in peri-eloquent language regions (Krieg et al. 2013; Tarapore et al. 2013a).

The functional maps generated with nTMS can be used for more than just localizing function. They also offer insights into the relative vulnerability of surround cortices and can be used for risk stratification (Lefaucheur and Picht 2016; Picht et al. 2012). Clinical studies are increasingly demonstrating the value of adding nTMS to the surgical management of brain tumors, with improvements seen in functional outcomes and EOR (Picht et al. 2016; Krieg et al. 2014a).

2.5.3 Limitations

While nTMS mapping is a promising new modality, there are several limitations that bear mentioning. The first of these relate to the precision of the navigation itself. The tolerance of registration on most modern nTMS systems is estimated at 2–3 mm; given that the guidance system is not frame-based, it is possible that the actual error is higher. Care must therefore be taken to ensure that preoperative maps match up with anatomical landmarks in the operating room: gyri and sulci, for example, and blood vessels can be used to ensure an accurate coregistration between the preoperative and the intraoperative findings.

Single-pulse nTMS for motor mapping, as described above, has been shown to be highly accurate. Limitations with this modality are similar to that of intraoperative cortical stimulation: namely, that cortical and subcortical lesions can interfere with the corticospinal tract (CST), making MEPs difficult or impossible to obtain. In the majority of these cases, patients will demonstrate signs of clinical weakness as well. This limitation can in fact be of great use; if preoperative mapping yields a difficult or unobtainable map, intraoperative DES will likely encounter the same difficulty. Additionally, if motor maps of inferior motor cortex are required, patients may complain of discomfort from associated temporalis contractions. In general, this discomfort is less than with rTMS because of the differences in protocol.

An inherent limitation in the specificity of nrTMS for language mapping is transsynaptic excitation of downstream (and, possibly, upstream) neuronal units. Neurophysiological and neuroimaging studies have shown that rTMS of a given brain region induces distributed activation of neural circuitry via transsynaptic spread, which follows established functional networks (Paus et al. 1997; Valero-Cabre and Pascual-Leone 2005; Bestmann 2008). Thus, behavioral effects may be a result of activation not in the target region but in a distant, functionally connected region. The "overcalling" seen in many nrTMS validation studies is likely a result of this limitation. Nevertheless, it should be pointed out that the overall nrTMS language map does reflect the distribution of DES language sites in both of the published series to date (Sanai et al. 2008; Picht et al. 2013; Tarapore et al. 2013b). Additionally, it seems to correlate with prior studies of nonnavigated rTMS mapping of language sites.

Another inherent limitation to both motor and language maps is the spread of the magnetic field itself. The figure-of-eight coil used in most modern systems generates a conical magnetic field. The field is therefore roughly circular at the cortical surface with a diameter of about 2 cm (and greatest intensity at the center with a sharp falloff at the edges) and tapers toward its apex, which occurs approximately up to 4.5 cm from the coil surface. As a result, the magnetic pulses might disrupt subcortical white matter tracts, while the overlying cortex is inappropriately identified as a site of motor function or language disruption.

Furthermore, a given neuron's orientation, volume, axonal and dendritic organization, and innate threshold affect the likelihood of a magnetic pulse generating an action potential (Pashut et al. 2011). Thus, nTMS-positive sites are not "points," that is, a misnomer; it is more accurate to say that they are regions and to be aware that closely approximated regions of positivity on the map may all be associated with a single eloquent cortical site.

Finally, the basic parameters of nrTMS stimulation, particularly with regard to language mapping, should be examined more systematically and thoroughly. It is possible that relatively small adjustments in the frequency or number of pulses could improve results (Hauck et al. 2015). Similarly, the timing of the onset of the pulse train is potentially important. In one published series, the pulse train was initiated just before the presentation of the stimulus in an object naming task, largely because that is the protocol used for DES (Tarapore et al. 2013b). It is possible,

however, that initiating the pulse train with or just after the stimulus might improve the specificity of nrTMS mapping (Krieg et al. 2014b; Sollmann et al. 2016). These variations in task and parameter must be methodically explored in future studies of nrTMS protocols.

2.6 Comparing and Contrasting Functional Imaging Techniques

Functional MRI, MEG, and nTMS each have particular strengths, which make them clinically useful in the correct situation. Similarly, each of these modalities has limitations that the clinician must keep in mind when ordering and interpreting results.

2.6.1 Temporal Considerations

The fMRI technique is, by far, the most widely used of these three functional imaging modalities. To many clinicians, the term "functional imaging" is synonymous with that of fMRI. It is in use worldwide, largely because of its accessibility—anyone with a reasonably modern MRI scanner can perform an fMRI study. Ironically, fMRI is one of the less well-suited functional studies for the purposes of presurgical mapping. The BOLD signal is 3° removed from neuronal activity and, as a result, the fMRI suffers from poor temporal resolution. While this limitation may not be of particular significance if the objective is simple localization of the primary motor cortex, it becomes much more important in localization of language cortex, where multiple cortical regions are involved and the interplay between those regions defines their functionality. MEG, on the other hand, is particularly well suited for defining cortical regions associated with language function. Because of its high temporal resolution, it can identify the temporal relationship between various cortical sites as well as the spatial relationship.

2.6.2 Spatial Considerations

One advantage to fMRI is its relative insensitivity to the location or orientation of neuronal sources. The fMRI technique can resolve deep brain sources, such as those in the basal ganglia, and it can superficial sources. MEG, on the other hand, has difficulty with deep sources because of the low signal to noise ratio inherent to MEG recording. Similarly, fMRI has no preference for the orientation of neuronal groups, while MEG picks up radially oriented sources than tangentially oriented sources. Of critical importance, also, is the fact that fMRI only detects cortical involvement in the functional brain. White matter connections, which are equally important, are not detected with fMRI.

Similar to MEG, nTMS is most effective at identifying relatively superficial cortical sites. The magnetic pulse of the nTMS coil is cone-shaped and tends to

penetrate to a depth of 2–3 cm with most standard machines. Beyond that depth, the magnetic field of an nTMS coil is usually too weak to generate an inductive current in the target neurons.

2.6.3 Vascular and Electromagnetic Artifacts

The fMRI data can be affected by abnormal/asymmetric vasculature. In the neurosurgical patient, abnormal vasculature is commonly encountered, especially in higher-grade brain lesions. Therefore, in those patients for whom accurate functional mapping is most vital, fMRI can be subject to artifact. This artifact can significantly reduce the reliability of the fMRI results and, on occasion, make them useless (Giussani et al. 2010). Neither MEG nor nTMS are subject to these vascular artifacts.

MEG, on the other hand, is particularly sensitive to electromagnetic artifact. Dental fillings, implanted hardware in the head/neck, pacemakers, deep brain stimulators, and aneurysm clips can all generate enough electromagnetic interference if the MEG recording is not useful for clinical purposes. It should be noted that some of these devices also preclude patients from obtaining an MRI; in contrast to an MRI, however, there is no danger to the patient if an implanted device is not compatible with MEG.

In contradistinction to fMRI and MEG, nTMS is largely resistant to artifact. Because it involves direct stimulation of the underlying brain, it is not subject to inaccuracies from vascular abnormalities or from implanted devices. It should be noted, however, that certain implanted devices such as aneurysm clips and deep brain stimulators are a contraindication for TMS in general.

2.6.4 Side Effects and Patient Participation

Both, fMRI and MEG, have similar side-effect profiles, in that they are completely noninvasive and do not involve any patient contact. Patients experience no additional sensation as a direct result of these studies. Patients can experience claustrophobia in an fMRI and, to a lesser extent, in an MEG, but these effects can usually be ameliorated with small doses of anxiolytic medication. If motor and/or language mapping is being performed, patient participation is required.

Although nTMS is technically noninvasive, it does require patient contact during the course of the study, and the patient experiences the sensation of stimulation throughout. Depending on the intensity, frequency, and location of stimulation, the experience can range from benign to quite painful. In particular, nrTMS at high frequency and intensity over the temporalis muscle can generate significant patient discomfort.

Because motor mapping with nTMS is accomplished with integrated EMG, no patient participation is required for this study. It can be performed in sleeping or anesthetized patients, as well as in patients with decreased cognitive status secondary to intracranial pathology (Chap. 15). It is also useful in small children (Chap. 12). Language mapping with nrTMS, similar to MEG and fMRI, requires patient participation in the form of picture naming or other language tasks.

2.6.5 Accuracy

In quantifying the accuracy of fMRI, MEG, and nTMS, one must first define the gold standard by which these techniques are judged. In the case of neurosurgical patients, this standard is DES in which an electrified electrode is placed directly on the cortical surface during surgery. In all other patients for whom DES maps are not available, the techniques can only be judged against one another, and their relative accuracy is more subjective.

Several papers have compared the accuracy of fMRI, MEG, and nTMS with DES, although, to our knowledge, no paper has compared all three modalities with DES. Preoperative fMRI-based maps of motor function have been extensively validated against DES, with high concordance rates (Tomczak et al. 2000; Lehericy et al. 2000; Jack et al. 1994). In maps of language function, on the other hand, fMRI has correlated poorly with DES-based cortical speech arrest sites, but it has demonstrated excellent correlation with the Wada test for language lateralization (Binder et al. 1996; Deblaere et al. 2004).

Similar to fMRI, MEG-based maps of motor and sensory function demonstrate relatively good concordance with intraoperative DES data. On average, the error distance between MEG-based and DES-based motor sites is ~8 mm, which is well within the tolerances of coregistration and spatial resolution of most MEG sensor arrays (Tarapore et al. 2012b). MEG also correlates poorly with DES-based cortical speech arrest sites, but can differentiate language laterality with accuracy comparable to the Wada test (Findlay et al. 2012; Tarapore et al. 2013a).

Of these three functional techniques, nTMS-based motor maps have the highest concordance rates with intraoperative DES motor maps, with error distances from 3 to 6 mm (Picht 2014). Not only is the colocation extremely reliable, but the sensitivity and specificity of nTMS-based motor maps approaches 100%. Therefore, if a site appears positive on nTMS, it will be positive on DES, and if a site is negative on nTMS, it will be negative on DES. This is of particular value when performing limited craniotomies that minimize cortical exposure, as it allows the surgeon to maintain confidence in a negative intraoperative map and obviates the need for exposing a positive DES control site. In comparing nrTMS-based language maps with those of DES, the results are less concordant. Preoperative nrTMS-based maps have high sensitivity (i.e., few false-negative sites) but have poor specificity (many false-positive sites), thus only allowing for mapping of language-negative brain areas. Although this profile is better than the opposite, it demonstrates the continued need for refinement of nrTMS-based language mapping protocols.

2.7 Conclusion

Functional neuroimaging is an integral component in the diagnosis and management of CNS neoplasms. In addition to the standard anatomical techniques, modern functional imaging provides insight into the functional status of the peritumoral environment. These techniques allow the treating clinicians to predict the

neurological sequelae associated with the observation or treatment of a specific lesion and to optimize treatment strategies to minimize neurological morbidity. In comparing the techniques of fMRI, MEG, and nTMS, care should be taken in study selection, as each of these studies has unique strengths and weaknesses. Thorough knowledge of the limitations inherent to these techniques is crucial to accurate interpretation of the results. Each of these modalities, applied singly or in combination will help to improve clinical outcomes in patients with brain tumors.

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Integration of Functional Data in the Clinical Workflow

3

Nico Sollmann, Sandro M. Krieg, and Bernhard Meyer

3.1 Introduction

The use of nTMS is rapidly increasing in neurosurgical departments worldwide. However, besides the pure visualization of mapping results on the cortex within the nTMS system, the proper integration of functional data provided by nTMS into the departments' workflow as well as the easy accessibility to these data is crucial for the acceptance of this new technique within the departments but also for the effective use of the unique information nTMS can provide. Thus, when newly implementing nTMS data into a neurosurgical department, several considerations are important:

- Integration into existing data management structures, such as the hospital information system (HIS), PACS, and neuronavigational infrastructure (Brainlab iPlan Net®, Medtronic StealthStation®, and others)
- Implementation into the clinical workflow of your cancer center but also your neurovascular center
- Teaching your staff on the potentials but also the limitations of nTMS
- Giving yourself, your staff, and your department enough time to learn how to use nTMS data effectively

The following chapter provides the results and experiences of 7 years of daily clinical use of nTMS data in our department. During this time we integrated nTMS data step by step into our electronic infrastructure and our clinical workflow (Fig. 3.1). As said, the smooth and easy accessibility to nTMS data is a crucial step on the track to gain acceptance among the surgeons of a neurosurgical department.

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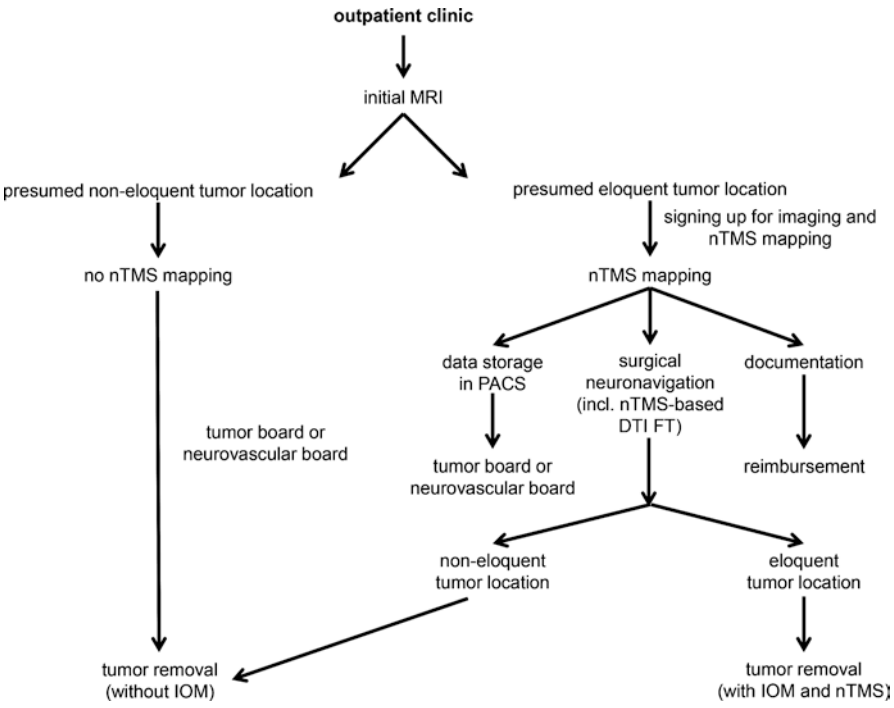

Fig. 3.1 Overview of the clinical workflow. This figure shows the different aspects of nTMS data integration into the clinical workflow, starting with presentation of a patient suffering from an intracranial lesion in the outpatient clinic. Indication for nTMS mapping is primarily based on the anatomic tumor location according to initial imaging

3.2 Integration into Existing Data Management Structures

3.2.1 Hospital Information System

Integration of nTMS data into the HIS can be easily achieved by a tailored software mask, which can be programmed individually by the manufacturer of the HIS (in our hospital: SAP SE, Walldorf, Germany; Fig. 3.2). This mask should include the following characteristics:

- Relevant patient details
- Aphasia grading
- Motor status at patient admission
- Current medication
- Suspected/confirmed tumor entity
- Tumor location
- Contraindications for nTMS (e.g., cardiac pacemaker, cochlear implant, deep brain stimulation electrodes)

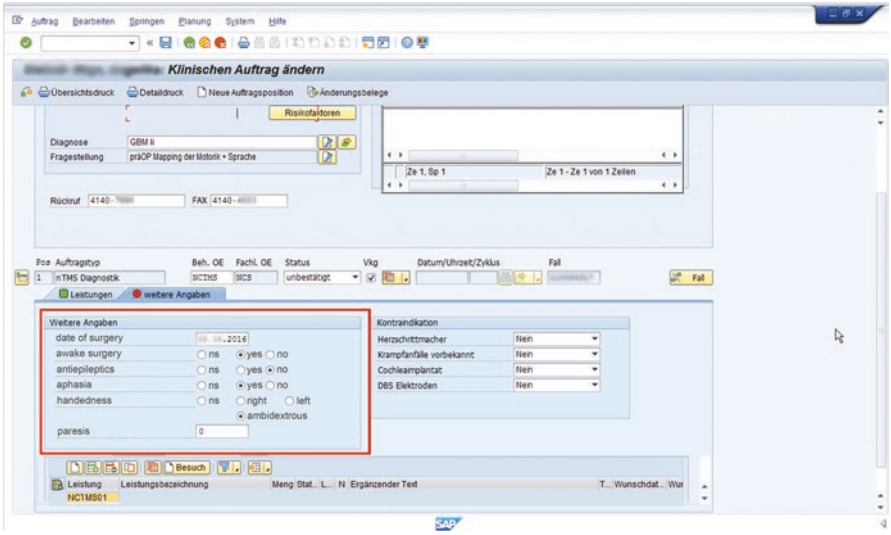

Fig. 3.2 Registration for nTMS mapping. Listing patients for nTMS mapping can be achieved by the use of a tailored software mask within the HIS. This software mask should include all relevant details required for thorough preparation and appointment planning. The *red box* contains some of the relevant details, which were translated from German for the ease of interpretation

- Availability of mandatory imaging data
- Special considerations concerning appointment planning

The appointment for nTMS mapping should be planned after any further MRI to have the latest imaging data available for the upcoming mapping. Furthermore, the nTMS mapping appointment can be integrated into the patient's clinical schedule within the HIS (Fig. 3.3), which increases clarity and avoids overlapping of examinations.

The HIS software mask can then be used for standardized documentation of the nTMS mapping as well as nTMS-based tractography (Fig. 3.4), including the following information:

- Stimulation details
- rMT
- Location of the motor hotspot in relation to the lesion
- Infiltrated cortical and subcortical structures
- Distances of the lesion to functionally relevant brain areas

Regarding language mapping, similar information about the distance between language-positive nrTMS spots or tracked subcortical language pathways and the lesion can be provided. Furthermore, error rates (ERs), which give information about the number of elicited naming errors during mapping divided by the number of stimulations, might be added to assess the frequency of naming impairment due

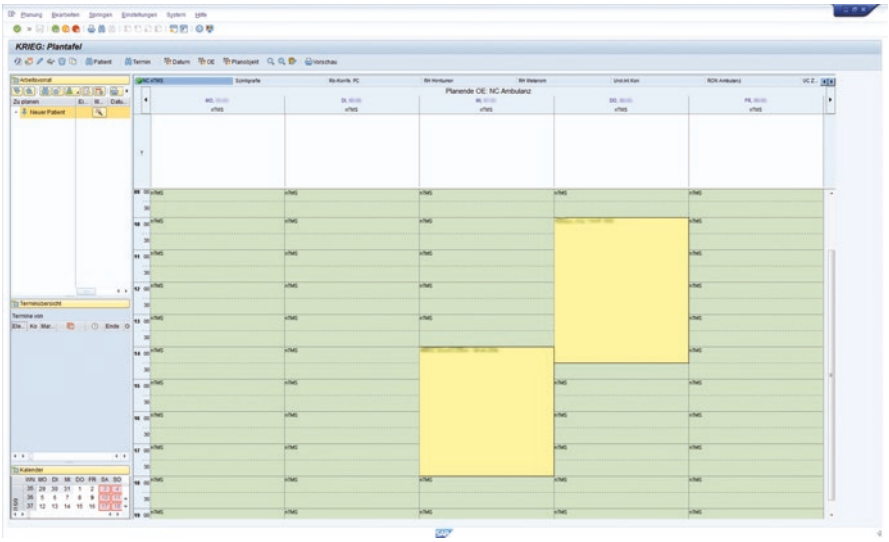

Fig. 3.3 nTMS appointment calendar. The nTMS mapping appointment can be integrated into a separate nTMS calendar within the HIS to facilitate clarity and to avoid overlapping with other examinations

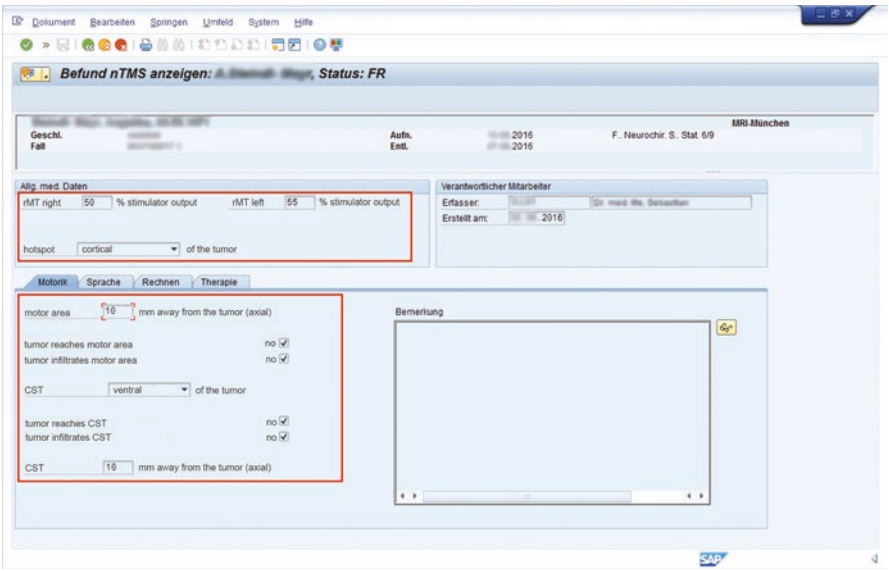

Fig. 3.4 Documentation. After the nTMS mapping, documentation of the results should be conducted within the HIS with respect to relevant parameters by the use of a tailored software mask. The final report should focus on the relation between the tumor and functional anatomy including nTMS-based tractography. Again, the details in the *red boxes* were translated from German for the ease of interpretation

to stimulation (Picht et al. 2013). In case that both hemispheres were mapped, ERs can be calculated for each hemisphere, thus allowing the determination of a hemispheric dominance ratio (HDR) by dividing the left-sided ER through the right-sided ER (Krieg et al. 2013; Ille et al. 2016; Sollmann et al. 2016b). The HDR can be used to assess the hemispheric language dominance in terms of nrTMS: an HDR >1 reflects left-sided dominance, whereas an HDR <1 indicates right-sided dominance (Chap. 10) (Ille et al. 2016; Krieg et al. 2013; Sollmann et al. 2016b).

The documentation of the nTMS mapping and nTMS-based tractography is saved within the patient's electronic folder, thus making it accessible during later follow-up examinations of the patient (Fig. 3.4). Furthermore, the report about the nTMS mapping can be printed and added to the paper chart of the individual patient.

3.2.2 Picture Archiving and Communication System

Mapping data should be transferred to the PACS for long-term storage. Moreover, the PACS provides easy accessibility to nTMS data and allows direct comparison between follow-up mappings. In terms of most nTMS systems, the data can usually be exported via the standard file format in medical imaging processing, which is the Digital Imaging and Communications in Medicine (DICOM) format (Bidgood and Horii 1992; Bidgood et al. 1997). For PACS storage, the dataset containing the nTMS spots projected on the original MRI sequence should be used to display functional maps in relation to the patient's anatomy (Fig. 3.5).

Fig. 3.5 PACS data storage. The dataset containing the nTMS spots, projected on the original MRI sequence, can be stored in the PACS and accessed via the PACS viewer (here: IDS7, Sectra AB, Linköping, Sweden). Motor-positive nTMS spots are depicted in *white*

In DICOM format, nTMS data can be transferred to the PACS of each hospital like every other imaging data from external institutions. Either this has to be done via the radiology department or one can personally upload the data via PACS integrator software (e.g., GEMED, Ulm, Germany). In most cases, a clinical order has to be generated via the HIS, which authorizes the upload to the PACS and the link between the new dataset and the individual patient case within the HIS.

As a third option, direct connection between the nTMS device and the PACS can be achieved (Makela et al. 2015). In this context, a graphical user interface can be programmed allowing for modification of nTMS data and transfer to the PACS via DICOM, which can further enhance clinical workflow (Makela et al. 2015). After correct upload of the dataset, it can be accessed by the use of the hospital's standard PACS viewer software (e.g., IDS7, Sectra AB, Linköping, Sweden) (Fig. 3.5).

3.2.3 Surgical Neuronavigation Systems

For the intraoperative use and also for advanced presurgical planning, nTMS data can be transferred to a surgical neuronavigation workstation (Brainlab iPlan Net®, Medtronic StealthStation®, and others) (Fig. 3.6). The dataset containing the

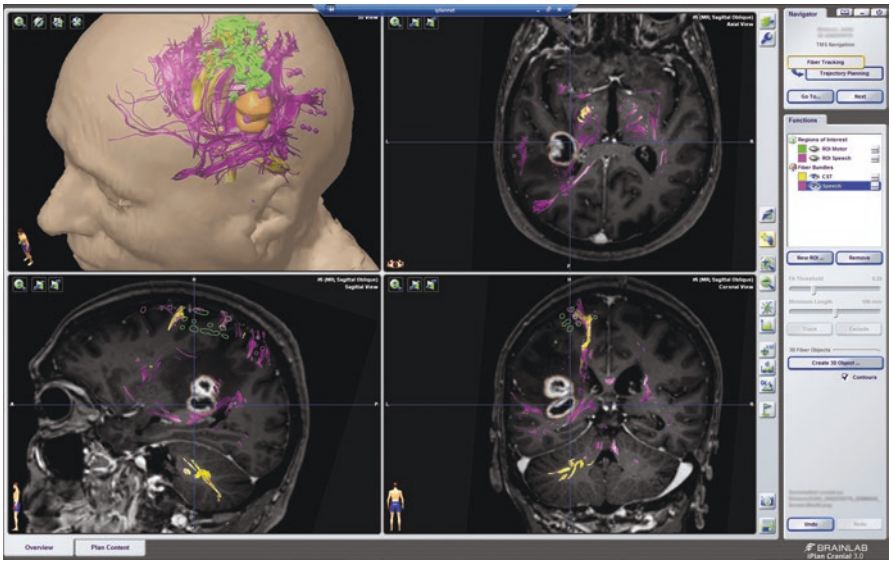

Fig. 3.6 Planning within the surgical neuronavigation system. The datasets containing nTMS spots can be implemented into surgical neuronavigation systems for preoperative resection planning, intraoperative guidance, and nTMS-based tractography (here: Brainlab iPlan Net®). The motor-positive nTMS spots are visualized in *green*, and the CST, delineated by nTMS-based tractography, is shown in *yellow*. Furthermore, language-positive nrTMS spots and subcortical language-related pathways are displayed in *pink*. The tractography results are visualized within the MRI sequence the nTMS mapping was conducted with. The tumor volume is shown in *orange*

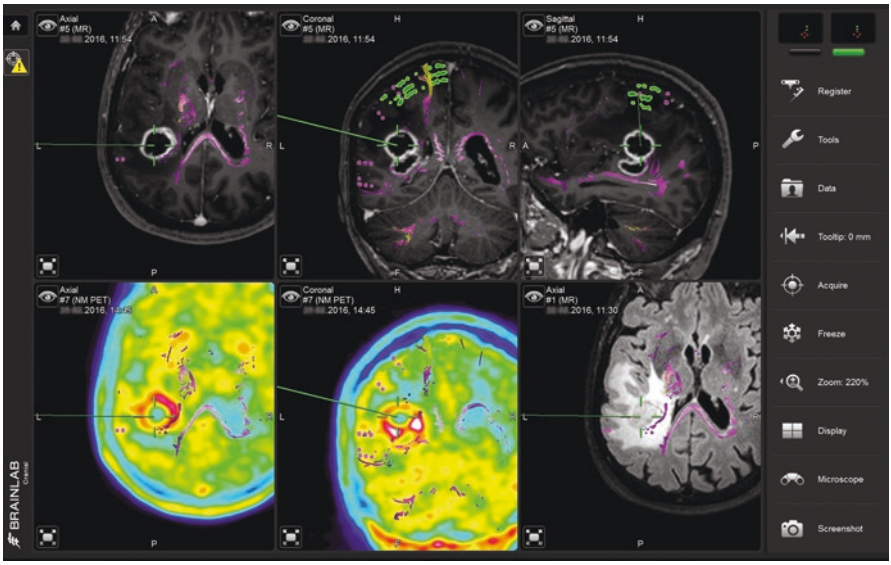

Fig. 3.7 Intraoperative use of the surgical neuronavigation system. After implementation of datasets containing nTMS spots and nTMS-based tractography, further MRI or PET sequences can be added to the image stack (here: Brainlab Curve). The motor-positive nTMS spots are visualized in *green* and the CST is displayed in *yellow*. Language-positive nrTMS spots and subcortical language-related pathways are depicted in *pink*

stimulation points without projection on the original MRI sequence can be fused with neuroimaging sequences of the respective patient. In this context, fusion is not limited to the initial MRI sequence the mapping was conducted with but can also include further anatomical, diffusion-weighted, and functional MRI sequences as well as CT or positron emission tomography (PET) sequences (Fig. 3.7), depending on the availability of sequences and the needs of the surgical team. After upload of all relevant imaging data and nTMS spots, the datasets need to be fused to create a common coordinate system with the nTMS spots being registered to the images. This fusion has to be highly accurate to guarantee that nTMS spots are presented at the original points of stimulation within the imaging sequences.

Most surgical neuronavigation systems allow for automatic and manual fusion. Automatic fusion is likely to result in optimal spatial overlap of datasets in cases where all imaging was acquired during the same scanning session without repositioning of the patient. However, manual fusion might be required in cases where automatic fusion does not lead to sufficient results. In general, fusion should be performed stepwise with respect to single datasets in order to detect any incorrect merging during the process. Moreover, all required datasets should be fused to one MRI sequence (preferably T1-weighted, contrast enhanced), which serves as a basis when performing consecutive fusions of multiple datasets.

The final accuracy of fusion should be visually assessed for all fused datasets. During this quality check, special attention should be paid to anatomical landmarks

that are easy to recognize and are regularly exported together with the nTMS spots (nasion, both crura of helix). At the minimum, the spatial overlap of the landmarks between the nTMS dataset and imaging sequences and the correct location of nTMS spots at the line of the cortical surface should be checked carefully. Correct fusion is a prerequisite for further reliable usage of the neuronavigation data. Then, the nTMS spots need to be transformed into objects via auto segmentation, thus allowing for switching the intraoperative visualization of nTMS data on and off according to the needs of the surgical team (Krieg et al. 2012).

Besides integration of nTMS spots into surgical neuronavigation systems and fusion with imaging sequences, most systems allow for further applications including tractography. To date, deterministic tracking algorithms using diffusion tensor imaging (DTI) sequences are most commonly provided by these systems, although other tracking approaches in combination with more advanced imaging have shown to increase the quality and reliability of tractography (Kuhnt et al. 2013; Caverzasi et al. 2016; Bucci et al. 2013). However, the current unavailability of other tracking approaches than diffusion tensor imaging fiber tracking (DTI FT) in most surgical neuronavigation systems and the rather long duration of image acquisition and tractography of the more elaborate approaches hamper clinical feasibility.

In patients with brain lesions affecting the motor system, data derived from nTMS motor mapping can be used to delineate the CST by DTI FT (Krieg et al. 2012; Frey et al. 2012; Conti et al. 2014; Forster et al. 2015; Weiss et al. 2015) (Chap. 6). Moreover, for patients harboring brain lesions in language-related areas, nrTMS language mappings can be used for DTI FT of subcortical language pathways (Negwer et al. 2016a, b; Sollmann et al. 2016c, d) (Chap. 9). In nTMS-based DTI FT of the CST or nrTMS-based DTI FT of language pathways, the entire sample or subsets of nTMS spots that gave rise to a specific event (e.g., motor responses above a certain threshold during motor mapping, naming errors of a certain category during language mapping) are commonly defined as regions of interest (ROI). Tractography is then performed with these nTMS-based ROIs to reconstruct subcortical fibers (Figs. 3.6–3.8). A detailed description of nTMS-based DTI FT for motor and language tracts is provided in Chaps. 6 and 9.

For the use of nTMS data within the surgical neuronavigation system, we recommend to define a standard coloring for each type of data to enhance understanding and clarity of data (Figs. 3.6–3.8). In our department, for instance, we use the following color-coding:

- Green: nTMS motor area (Chap. 5)
- Yellow: CST according to nTMS-based DTI FT (Chap. 6)
- Pink: nrTMS language area (first acquired language) and corresponding language pathways according to nrTMS-based DTI FT (Chaps. 8 and 9)
- Purple: nrTMS language area (second acquired language) and corresponding language pathways according to nrTMS-based DTI FT
- Red: nrTMS language area (third acquired language) and corresponding language pathways according to nrTMS-based DTI FT

Fig. 3.8 Patient consultation after mapping and nTMS-based tractography. The nTMS mapping and nTMS-based tractography results can be visualized during patient consultation in the outpatient clinic (here: Brainlab BUZZ® and Brainlab Elements). Motor-positive nTMS spots are visualized in *green*, and language-positive nTMS spots are *pink*. The CST, delineated by nTMS-based tractography, is shown in *yellow*, and language-related pathways are displayed in *pink*. The tumor volume is shown in *orange*

– Blue: nrTMS area involved in arithmetic processing and corresponding subcortical tracts according to nrTMS-based DTI FT (Chap. 11)
– Orange: lesion to be resected

In addition to the intraoperative use, the integration of functional data into surgical neuronavigation systems can also be used for detailed surgical planning as well as patient consultation in the outpatient clinic (e.g., via Brainlab BUZZ®, Medtronic StealthViz®, and others) (Fig. 3.8). The detailed visualization of functionally relevant anatomy helps the patients to understand the surgical problem and the risks and chances associated with the surgical treatment of the lesion.

3.3 Workflow

3.3.1 Indication for nTMS Mapping

Indication for nTMS mapping is primarily based on anatomical tumor location according to MRI (Picht 2014; Lefaucheur and Picht 2016; Ottenhausen et al. 2015). Favorably, nTMS mapping should be performed before discussing the individual patient case in an interdisciplinary tumor or neurovascular board (Fig. 3.1). In this context, motor mapping by nTMS should be scheduled for lesions that are presumably located within motor-eloquent brain areas (infiltration or compression

of the anatomically suspected motor cortex and/or proximity of the tumor to the CST). Analogously, nrTMS language mapping should be carried out when language-related brain areas are affected (infiltration or compression of the anatomically suspected language cortex and/or proximity of the tumor to subcortical language pathways). However, due to widespread functional networks, interindividual variability in location of cortical and subcortical functional structures, and plasticity-associated shifting of functional areas, indication for nTMS mapping can be justified in most cases of presumable affection of functionally relevant structures (Picht 2014; Lefaucheur and Picht 2016; Ottenhausen et al. 2015). Furthermore, even transient functional impairment (e.g., aphasia or paresis) can be a sign of tumor location close to eloquent cortex or tracts although anatomical considerations would not have necessarily suggested eloquent location.

3.3.2 Registration for Imaging and nTMS Mapping

After the decision for nTMS mapping has been made, a standardized workflow can be followed that starts with signing the patient up for navigational MRI sequences (if not already available) and nTMS mapping via the HIS (Figs. 3.1 and 3.2). Adequate MRI sequences are a prerequisite for mapping by nTMS, and the interval between MRI acquisition and the mapping appointment should be kept to a minimum to guarantee mapping with respect to the current tumor extent. A 3D gradient echo sequence (slice thickness: 1 mm) with contrast enhancement is recommended. DTI sequences (e.g., 15 or 32 orthogonal diffusion directions) can be added for tractography reasons.

The patient listing for nTMS is visible within the HIS, which allows for arrangement of the mapping session by the nTMS team. The arranged appointment should be added to the patient's electronic folder and the nTMS calendar (Fig. 3.3). While the first order should be made by the physician who examined the patient, arrangement of the appointment for mapping and further documentation can be done by the nTMS technician.

3.3.3 Data Preparation and Export

After mapping and post hoc analysis of the mapping data (Chaps. 5 and 8), the nTMS system commonly generates files with stimulation locations that can be exported in DICOM format (Bidgood and Horii 1992; Bidgood et al. 1997). During the post hoc analysis, the investigator determines which stimulation spots are transferred from the nTMS software to exportable DICOM files. For motor and language mapping, only motor-positive or language-positive stimulation spots are commonly taken into account. However, most nTMS systems also allow for inclusion of other subsets of stimulation points.

Regarding the selected subset of stimulation points for export, two types of DICOM image stacks can be produced: (1) datasets containing the stimulation points, projected on the original MRI sequence the mapping was conducted with,

and (2) datasets containing the stimulation points and key anatomical landmarks only (nasion, both crura of helix). Importantly, the coordinate space of the stimulation points equals that of the original MRI sequence in both cases, which is a prerequisite in terms of precision for later fusion of different datasets within the surgical neuronavigation system. The transfer of mapping data to other devices can be accomplished via portable devices (e.g., flash drive, external hard drive), intranet, or direct connection of the nTMS system to the PACS (Makela et al. 2015).

3.3.4 Data Storage in PACS

For long-term storage, datasets derived from nTMS mappings should be transferred to the PACS (Fig. 3.5). After storage, these datasets can be called up on every computer connected to the hospital's PACS, thus allowing for presentation of nTMS maps in tumor or neurovascular boards together with other imaging or clinical data relevant for surgical decision-making.

3.3.5 Integration into Surgical Neuronavigation Systems

To use nTMS data for surgical planning and resection guidance or visualization in combination with further imaging data, the DICOM image stack containing the stimulation points selected for export can be copied to a surgical neuronavigation workstation or even a separate network, such as iPlan Net® (Brainlab, Munich, Germany). The patient's navigational sequences, including nTMS-based DTI FT, can be used in the operating room during surgery but also for patient consultation in the outpatient clinic (e.g., via Brainlab BUZZ®, Medtronic StealthViz®, and others) (Fig. 3.8).

3.3.6 Documentation

The results of the mapping including nTMS-based tractography need to be documented for each patient in a structured way as described above (Fig. 3.4). Like initial registration for mapping, this can be managed via a tailored software mask within the HIS.

3.3.7 Illustrative Clinical Case

Initially, the 84-year-old female patient presented with transient aphasia. No further neuropsychological or motor deficits were reported. CT imaging showed a left-sided temporodorsal, subcortical space-occupying lesion.

After referral to our neurosurgical department, the patient underwent PET-MRI including 3D gradient echo sequences (with and without contrast enhancement) and

DTI. MRI confirmed a left-sided subcortical lesion (maximum diameter: 3.0 cm) within the temporoparietal junction, which was contrast-enhancing and suspected to be a high-grade glioma. Listing for nTMS motor and language mapping via the HIS was done due to presumed eloquent tumor location.

Motor and language mapping were carried out within the same session 3 days before surgery on an outpatient basis according to standardized stimulation protocols. In this context, language mapping in combination with an object-naming task was conducted, using 100% of the individual rMT and 5 Hz/5 pulses (Rosler et al. 2014; Krieg et al. 2013, 2014b). Both hemispheres were examined consecutively, and post hoc evaluation of the mapping data was carried out to detect motor- and language-positive nTMS spots for DICOM export. Separate datasets (containing either motor- or language-positive nTMS spots) were then transferred from the nTMS system to an external workstation, which was connected to the surgical neuronavigation system, HIS, and PACS. For storage, the datasets containing positive stimulation spots of the tumor-affected hemisphere, projected on the original MRI sequence, were sent and integrated into the PACS via PACS integrator software (GEMED, Ulm, Germany) (Fig. 3.5). Furthermore, datasets with positive stimulation spots only (without projection on the original MRI sequence), derived from mapping of the tumor-affected hemisphere, were integrated into the surgical neuronavigation system for surgery planning and nTMS-based DTI FT (iPlan Net®, Brainlab AG, Munich, Germany). In this context, MRI and PET-MRI sequences were added to the positive nTMS spots, and nTMS-based DTI FT was carried out separately for subcortical motor and language pathways after image fusions and ROI generation (Figs. 3.6 and 3.7). In this context, nTMS-based DTI FT of the CST was carried out with a minimum fiber length of 100 mm and a fractional anisotropy value of 0.2 (Figs. 3.6 and 3.7) (Krieg et al. 2012). Concerning tractography of subcortical language-related pathways, 100 mm and 0.1 were used (Figs. 3.6 and 3.7) (Negwer et al. 2016a). The resulting neuronavigation sequence was saved and used for preoperative approach planning and during surgery for tumor resection. The final mapping report was prepared in the software template of the HIS by a medical doctor of our nTMS group and saved within the patient's electronic chart.

3.4 Potentials and Limitations

In most neurosurgical departments, nTMS mappings are currently conducted by medical doctors in collaboration with medical technicians. Importantly, thorough training by experienced staff and the nTMS manufacturers should precede all nTMS applications to ensure accurate and standardized mappings, which can generate data beneficial for surgery and patient consultation.

Although the availability of reliable nTMS mapping data can shorten intraoperative DES mapping significantly, it is not meant to replace DES or IOM. In contrast, nTMS is a helpful adjunct for every IOM program rather than a competing modality. In cases of presumed eloquent tumor location, IOM starts but does not end with nTMS. Together they enable proper patient selection and approach planning, thus

leading to faster surgery and improved functional and oncological outcome (Frey et al. 2014; Krieg et al. 2014a, 2015; Sollmann et al. 2015; Picht et al. 2016).

Additionally, we have to understand that nTMS can primarily map cortical regions that are close to the surface and therefore reachable by the magnetic field. This means that we are unable to map temporomesial and frontobasal gyri as much as we are unable to map brain areas covered by large arachnoid cysts or even large meningiomas. This is especially important because we cannot completely rule out eloquent function within these regions although the stimulation would not show us any elicited motor responses or language impairment. Especially nTMS systems calculating the induced electric field in every depth of the gyrus of interest avoid these potentially dangerous issues.

3.5 Learning Curve

Overall, nTMS mappings reflect detailed investigations, which should only be carried out by fully trained examiners. Yet, learning curves have shown to be comparably steep, with possible reductions of the time needed for preparation and post hoc analysis by 78.8% and by 59.6% for motor mapping in the course of 12 patient mappings (Sollmann et al. 2016a). Hence, when nTMS is used on a regular basis after initial training by the manufacturer, mappings can be carried out with increasing speed while accuracy is enhanced simultaneously (Sollmann et al. 2016a). Mapping speed and accuracy seem to be essential for successful implementation and acceptance of nTMS in the daily clinical routine.

Nonetheless, it is not only the nTMS examiner who experiences a learning curve. It can be quite elaborate to introduce a new MRI protocol needed for nTMS to the hospital's radiology department (including the correct navigational and DTI sequences), but also to establish a standardized data transfer depending on the restrictions of the hospital's information technology department or the PACS administrators. If one faces severe data access restrictions, a manual data transfer might be necessary.

Moreover, neurosurgeons also have to get used to the new data and have to learn how to use it. We not only have to learn that we are now able to use the functional anatomy for approach planning but we also need to gain trust that the nTMS data, presented via the surgical neuronavigation system, are sufficiently accurate so that we can significantly shorten the intraoperative time needed for DES mapping in many cases. Moreover, if using monitoring via DES strip electrodes, phase reversal is no longer required since nTMS motor maps directly guide us to the motor cortex.

3.6 Conclusion

Smooth integration of nTMS into clinical routine enhances the availability and usefulness of nTMS applications in neurosurgical centers. This integration can be achieved by using mostly standard devices and standard software. However, although the learning curves of most parts of nTMS implementation are steep and

the required electronic infrastructure is already present, we still need to be aware of various issues to initially develop solutions to manage resulting problems immediately.

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Safety Considerations of the Use of TMS

4

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4.1 Introduction

Since its introduction in 1985 by Barker et al., the international scientific community has observed a rapid increase of TMS in studying cognition, brain–behavior relationship, and pathophysiology of various neurologic and psychiatric disorders. The development of new coils, new stimulus paradigms (e.g., patterned repetitive TMS), the introduction of neuronavigation, and the real-time integration of TMS with EEG, PET, and fMRI have rendered research and clinical studies more accurate, more insightful, and of greater clinical value. These developments have also allowed investigating non-motor areas of the brain and testing the therapeutic impact of TMS. In fact, in the last decade, a large number of studies and clinical trials have demonstrated potential therapeutic applications of TMS. Recent guidelines can be found in the literature covering specific aspects of TMS, such as theoretical and physiological aspects (Rossini et al. 2015), methodology (Groppa et al. 2012), and therapeutic applications (Lefaucheur et al. 2014).

As in these years, the number of applications of TMS has grown impressively; the scientific and medical community has felt the need to evaluate the safety record of research studies and clinical applications of TMS and rTMS. The first safety precautions and practice recommendations were established by the consensus conference held at the National Institutes of Health in June 1996 and summarized in *Clinical Neurophysiology* (Wassermann 1998) and were subsequently adopted by

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the International Federation of Clinical Neurophysiology (IFCN) (Hallett et al. 1999). Green et al. (1997) were the first to itemize ethical considerations on the application of TMS to health and disease during the initial stages of rTMS testing, and later several publications addressed these aspects (Wolpe 2002; Mashour et al. 2005; Illes et al. 2006; Steven and Pascual-Leone 2006). After about 10 years from the publication of the first safety guidelines, a large group of worldwide experts, including neurologists, neurophysiologists, psychiatrists, experimental psychologists, cognitive neuroscientists, physicists, engineers, representatives of TMS equipment manufacturers, and representatives from various world regulatory agencies, have met in Siena in March 2008, on behalf of IFCN, with the objective to revise all the available material regarding the safety of TMS that appeared in the literature since 1996 to the meeting date. A consensus had been reached for most of the treated items regarding safety, as well as ethical issues and recommendations for the use of TMS in research and clinical settings, and these aspects had been summarized in a new document that appeared in the late 2009 on *Clinical Neurophysiology* (i.e., the official journal of IFCN) (Rossi et al. 2009).

The 2009 updated guidelines had reviewed issues of risk and safety of conventional and emerging TMS protocols, also covering recommended limits of stimulation parameters and other important precautions, monitoring of subjects, expertise of the rTMS team, and ethical issues. From the consensus meeting time, all safety tables published in that article are still valid and not formally updated yet: a few new aspects regarding safety have emerged, suggesting that safety tables updated in 2009 were basically successful in preventing major adverse events of the procedure. Therefore, the present chapter will be a short summary of the most relevant safety aspects that have to be taken into account when using TMS in a diagnostic setting and will highlight those new aspects that have emerged from 2009 up to the end of 2016.

4.2 Contraindications and Precautions

The report of the TMS safety study group in 2009 provided detailed guidelines, covering safety issues of single-pulse and repetitive TMS in healthy individuals and patients. Examining the large amount of TMS studies carried out before the publication of the 2009 guidelines, the authors stated several considerations for which full consensus was reached that are still widely acceptable and are briefly outlined below.

The unique absolute contraindication to TMS/rTMS currently remains the presence of metallic hardware in close contact to the discharging coil (cochlear implants, internal pulse generator, cerebrospinal fluid shunt, or medication pumps), due to the risk of inducing malfunctioning of such implanted devices. Some circumstances are associated to an increased (or uncertain) risk of inducing the most serious adverse TMS-related event, i.e., epileptic seizure, and concern conditions linked to:

1. The stimulation protocol: application of any “novel paradigm” (i.e., not a classical method of HF/LF rTMS, performed with a flat figure-of-eight coil and biphasic

pulse waveform) and of conventional HF rTMS protocol with parameters of stimulation (intensity, frequency, train length, or inter-train duration) exceeding the known 2009 safety limits [see the appropriate section of this chapter].
2. Disease or patient's condition: personal history of epilepsy (untreated patients with one or a few past episodes), or treated patients; vascular, traumatic, neoplastic, infectious, or metabolic lesion of the brain, even without history of seizure, and without anticonvulsant medication; administration of drugs that potentially lower seizure threshold (for a full list, see Sect. 5.3 in Rossi et al. 2009), without concomitant administration of anticonvulsant drugs which potentially protect against seizure occurrence; sleep deprivation and alcoholism.

Other instances associated to an increased (or uncertain) risk of other adverse events are related to particular conditions including implanted brain electrodes (cortical or deep brain electrodes) [see the appropriate section of this chapter] and pregnancy. Single- or paired-pulse TMS or conventional LF or HF rTMS protocol including none of the previous conditions and with parameters of stimulation within the 2009 safety limits is to be considered "free of risk."

Summarizing, with the exception of the implanted devices, all the other conditions should be considered only relative contraindications, and the risk–benefit of the procedure should be carefully considered before starting any TMS study. For this reason, a short safety checklist should be used to screen patients before they undergo TMS investigations, including a history of seizures or syncope, brain diseases or medications associated with increase seizure risk, the presence of implanted biomedical devices, and pregnancy. To this purpose, an updated version of the questionnaire for the screening of patients before TMS investigations published by Rossi et al. (2011) is here reproduced in full, given its great utility in clinical and research practice.

Screening 13-item questionnaire for TMS candidates:

1. Do you have epilepsy or have you ever had a convulsion or a seizure?
2. Have you ever had a fainting spell or syncope? If yes, please describe on which occasion(s)?
3. Have you ever had a head trauma that was diagnosed as a concussion or was associated with loss of consciousness?
4. Do you have any hearing problems or ringing in your ears?
5. Do you have cochlear implants?
6. Are you pregnant or is there any chance that you might be?
7. Do you have metal in the brain, skull, or elsewhere in your body (e.g., splinters, fragments, clips, etc.)? If so, specify the type of metal.
8. Do you have an implanted neurostimulator (e.g., deep brain stimulation (DBS), epidural/subdural, vagus nerve stimulator (VNS))?
9. Do you have a cardiac pacemaker or intracardiac lines?
10. Do you have a medication infusion device?
11. Are you taking any medications? (Please list.)
12. Did you ever undergo TMS in the past? If so, were there any problems?
13. Did you ever undergo MRI in the past? If so, were there any problems?

4.3 Considerations on Dosing TMS

In 1998, Wassermann determined for the first time the safety limits of the four key parameters that define rTMS trains, i.e., intensity, frequency, train duration, and inter-train interval. Determining the maximum safe durations of single trains of rTMS at various frequencies and intensities (Table 4.1; Wassermann 1998), these limits have shown great efficacy in preventing seizure, spread of excitation, or after-discharges of EMG activity in the following years, both in normal subjects and in patients with neurological and psychiatric diseases, despite the fact that such guidelines were based on a relatively restricted sample of normal subjects and considered only conventional rTMS. In 2008, the safety consensus group reevaluated these safety limits, restricting for research/clinical purposes safe intensity range of stimulation from 100–220% to 90–130% of rMT, using a figure-of-eight coil (Table 4.2; Rossi et al. 2009): for studies eventually exceeding this limit (i.e., from 140% to 220% of rMT), the previous guidelines remain still valid.

Table 4.1 Safe durations of trains of rTMS at various frequencies and intensities

Frequency	Intensity (% of MEP threshold)												
(Hz)	100	110	120	130	140	150	160	170	180	190	200	210	220
1	>1800	>1800	360	>50	>50	>50	>50	27	11	11	8	7	6
5	>10	>10	>10	>10	7.6	5.2	3.6	2.6	2.4	1.6	1.4	1.6	1.2
10	>5	>5	4.2	2.9	1.3	0.8	0.9	0.8	0.5	0.6	0.4	0.3	0.3
20	2.05	1.6	1.0	0.55	0.35	0.25	0.25	0.15	0.2	0.25	0.2	0.1	0.1
25	1.28	0.84	0.4	0.24	0.2	0.24	0.2	0.12	0.08	0.12	0.12	0.08	0.08

Numbers preceded by > are the longest durations tested. No after discharge or spread of excitation has been encountered with single trains of rTMS at these combinations of stimulus frequency and intensity

This table from Wassermann 1998, shows the maximum safe durations of single trains of rTMS at various frequencies and intensities (corresponds to Table 3 in Wassermann 1998)

Table 4.2 Safety limits of the safety consensus group from 2008

	Intensity (% of MT)				
Frequency (Hz)	90%	100%	110%	120%	130%
1	>1800[a]	>1800	>1800	>360	>50
5	>10	>10	>10	>10	>10
10	>5	>5	>5	4.2	2.9
20	2.05	2.05	1.6	1.0	0.55
25	1.28	1.28	0.84	0.4	0.24

Maximum safe duration (expressed in seconds) of single trains of rTMS. Safety defined as absence of seizure, spread of excitation or afterdischarge of EMG activity. Numbers preceded by > are longest duration tested. Consensus has been reached for this table

In 2008, the safety consensus group restricted the safe intensity range to 90–130% of rMT for figure-of-eight coils. As in Table 4.1, this table provides maximum safe durations of single trains of rTMS at various frequencies and intensities based on literature review and expert consensus (corresponds to Table 4 in Rossi et al. 2009)

[a]In Japan, up to 5000 pulses have been applied without safety problems (communication of Y. Ugawa)

It should be remarked here that the above-suggested safety parameters are all derived from rTMS applied to the motor cortex: for the individualization of intensity of stimulation, almost all the published studies refer to the classical definition of the rMT, i.e., the minimal intensity required to elicit an EMG response of at least 50 μV with 50% probability in a fully relaxed muscle (Rossini et al. 1994, 2015), even when brain regions outside the motor cortex are stimulated, although the exact relationships between the excitability of motor and non-motor brain regions are still to be determined. A reasonable starting point for safe rTMS applications on cortical areas outside the motor cortex derives from the observation that the threshold for induction of afterdischarges is lowest in the motor cortex compared to other cortical areas when stimulated electrically (Penfield and Jasper 1954). However, definitive safety tables for rTMS application outside the motor cortex are still lacking and need future research. Phosphene threshold (PT), i.e., the minimal intensity required to induce a phosphene in the contralateral visual hemifield (Marg and Rudiak 1994), could be more appropriate to individualize the intensity of stimulation when targeting visual areas; however, the determination of PT is usually difficult to be obtained in half of the subjects, and an exact relationship between rMT and PT (and also the threshold for TMS activation of other nonmotor areas) is currently unknown.

In the last decade, the rapid and large development of rTMS for the possible treatment of several neurological and psychiatric diseases (Lefaucheur et al. 2014) has raised newer safety issues. In fact, the repeated application of rTMS in a great variety of clinical settings introduced additional dosing parameters that describe the cumulative exposure to rTMS, i.e., total pulses per session, sessions per day, days per week, weeks per acute course, and maintenance frequency. Furthermore, several studies explored the (sequential or simultaneous) combination of different protocols of stimulation (HF rTMS, LF rTMS, theta burst stimulation (TBS), paired associative stimulation (PAS)). These variables, together with advances in terms of technology (new forms of coils and magnetic field geometry, neuronavigation, integration with EEG, and neuroimaging), should be strongly considered for future safety investigations.

4.4 Adverse Events

4.4.1 Seizures

Seizures are the most serious possible adverse event related to TMS. In almost three decades of TMS experiments and for hundreds of thousands examined subjects, only few cases of TMS-induced seizures have been reported, and the vast majority of seizures were induced during rTMS (Rossi et al. 2009). The risk to induce a seizure with single-pulse TMS is very low: it has been estimated that less than 5% of the known TMS-related seizures occurred during single-pulse TMS studies and always in subjects having epileptogenic brain lesions or under proactive medication (Groppa et al. 2012).

Repetitive TMS can induce seizures when pulses are applied with relatively high frequencies and short interval periods between trains of stimulation. In theory, induced seizures might occur during two different periods associated with stimulation: (1)

during or immediately after trains of rTMS and (2) during the aftereffects due to the modulation of cortical excitability (i.e., kindling effect; see Wassermann 1998), but to date there is no evidence that the latter event has ever occurred.

Up to the end of 2008, a total of 16 cases of seizures were identified (Rossi et al. 2009). Seven of these cases were reported before the publication of the 1998 safety guidelines and the recommended parameters of stimulation (intensity, frequency, and train duration) according to these guidelines. Nine of these cases occurred in the following years and were reported in the 2009 safety guidelines. Four of the new seizures (two following single pulse and two following rTMS) induced by TMS since publication of the prior 1998 guidelines appear to have been induced by "safe" stimulation parameters: three of these four seizure episodes occurred in patients taking proepileptogenic medications (Figiel et al. 1998; Haupts et al. 2004; Tharayil et al. 2005), one of these four cases occurred in a subject with a known structural brain pathology (Haupts et al. 2004), and, furthermore, two of the four cases may represent non-epileptic events (pseudoseizure or convulsive syncope) (Figiel et al. 1998; Nowak et al. 2006; Epstein 2006). The other four cases of accidental seizures reported in the 2009 safety guidelines occurred in studies using parameters outside the 1998 safety guidelines: three of these four instances of seizures occurred in patients taking proepileptogenic medications or following sleep deprivation (Bernabeu et al. 2004; Rosa et al. 2004; Prikryl and Kucerova 2005), and one of the four cases may represent a non-epileptic event (Conca et al. 2000). The last of the nine cases is the only one documented seizure induced by TBS, described by Obermann and Pascual-Leone (2009) in a 33-year-old healthy man with no risk factors for epilepsy (for safety consideration about TBS, see the apposite section). Since the publication of 2009 safety guidelines up to now, only a few cases of TMS-related seizures have been reported: one case occurred because of a clear violation of the suggested 2009 safety guidelines (Edwardson et al. 2011); three cases occurred in patients with major depression under proactive medication (Chiramberro et al. 2013; Boes et al. 2016; Cullen et al. 2016) and in two of these three cases during the application of deep brain TMS protocols with the new H-shaped coils (Boes et al. 2016; Cullen et al. 2016); another case occurred in a patient with an anaplastic oligoastrocytoma with a focal seizure induced by preoperative nTMS (Groiss et al. 2017); finally, another two "discussed" cases reported a TMS-induced seizure from a cortical focus different from the stimulation site (Vernet et al. 2012) and a delayed seizure after LF rTMS in a chronic stroke patient (Agosta et al. 2016; Kumar et al. 2016; Nitsche 2016).

Considering the large number of subjects and patients who have undergone TMS studies since 1998 and the small number of seizures (as reported above), it can be stated that the risk of (single-pulse, repetitive, or patterned) TMS to induce seizures is certainly very low. However, it should be emphasized that for all those studies based on TMS protocols that are not sufficiently tested yet from a safety point of view (as TBS) such as protocols that use a combination of parameters of stimulation close to the safety limits of the published guidelines, experiments that contemplate the use of new technological devices (as H-shaped coils), and all the clinic and research studies in patients with neurological and psychiatric conditions of increased risk, neurophysiological monitoring is strongly recommended. This should be done

according to the technical indications (measuring the spread of excitation to neighboring cortical areas or possible manifestations of EEG afterdischarges) provided by Rossi et al. (2009).

4.4.2 Syncope

A vasodepressor (neurocardiogenic) syncope is a common reaction to anxiety and psychophysical discomfort that may occur more often than epileptic seizures during TMS testing and treatment, including TBS (Grossheinrich et al. 2009), as well as during other noninvasive or minimally invasive medical procedures. Although there are no systematic studies addressing the incidence of this phenomenon during TMS, syncope is a common experience in many labs.

The cardinal feature to distinguish syncope from seizure is rapid recovery of full consciousness within a few seconds and not minutes (Lin et al. 1982; Caplan 2000). The premonitory complaint that "I need to lie down" or "I need air," narrowing and blacking out of the visual field, sensations of heat, bradycardia, and loss of peripheral pulses also favor circulatory collapse. Visceral distress, sweating, pallor, nausea, and dizziness are frequent symptoms. Gastrointestinal symptoms occur in partial epilepsies as well, but their incidence in seizures provoked by TMS is unknown.

Differential diagnosis between syncope and seizure may be difficult in case of positive phenomena. The former may include phenomena considered typical of seizures: tonic contractions, jerking, vocalizations, orofacial and motor automatisms, brief head or eye version, incontinence, hallucinations, and injuries from falling. Such episodes can be difficult to distinguish from epileptic events, although tongue biting and loss of urine are often lacking. Upward eye deviation is common in vasovagal syncope but rare in partial seizures unless they progress to generalized convulsions. It is important to remember that patients who develop syncope under TMS have often experienced similar episodes in the past.

Initial measures for suspected seizures and syncope are identical. TMS should be terminated immediately and the subject assisted in controlled reclining without impact. Airway breathing and circulation should be assessed. Unless tonic-clonic seizure activity occurs, the subject should be turned on one side to help clear the airway and avoid aspiration. Subjects who convulse should be turned on one side as soon as movement ceases and maintained in that position until recovery of awareness. Delayed recovery of normal consciousness beyond 30 s following a seizure mandates further medical evaluation.

4.4.3 Minor Side Effects

Minor adverse effects include headache (28–40%) (Machii et al. 2006; Loo et al. 2008), temporary acute hearing reduction (9%) (Pascual-Leone et al. 1991; Loo et al. 2001), and pain (39–40%) (Machii et al. 2006; Loo et al. 2008). Most of the

subjects do not complain about discomfort, especially when they are familiarized with the TMS procedure. Some may experience surprise looking at their hand/arm twitching; some may feel a local mild discomfort under the stimulating coil or slight tongue paresthesia during TMS of high intensity delivered on the midline for activation of lower limb corticospinal neurons. Both patient and examiner should always wear earplugs during diagnostic TMS to prevent transient auditory threshold changes, which are more likely to occur during rTMS but are theoretically possible even with single-pulse application.

4.5 Safety Issues of Methodological and Technical Advancements

4.5.1 Patterned Repetitive TMS

Since its introduction (Huang et al. 2005), the use of TBS has gradually grown in the last few years, as the aftereffects are similar to those induced by conventional rTMS interventions but can be obtained by short trains of stimuli at high frequency repeated at intervals of 200 ms. For this reason, TBS has the theoretical potential of conferring an even higher risk of seizure than other rTMS protocols because it delivers high-frequency bursts. At the time of the consensus meeting of 2008, because the absence of specific literature and of recommendations for the maximum duration or intensity of stimulation when applying TBS, safety guidelines could not be provided. At that time, there was only one study specifically addressing the safety of TBS in 24 healthy subjects who received stimulation on left dorsolateral and medial prefrontal cortices (Grossheinrich et al. 2009) that noted no serious adverse effects (except from lipotimic-like reactions in three subjects). Two years later, Oberman et al. (2011) performed a meta-analysis of 67 studies published from May 2004 to December 2009 in which TBS was applied, calculating the crude risk of adverse events in a cohort of 1040 subjects/patients (healthy controls and clinical patients with a great variety of neurological or psychiatric diagnosis). The majority of adverse events attributed to TBS were mild and occurred in 5% of subjects, including above all headache and neck pain. The crude risk for mild adverse events was estimated to be 1.1%, while that of seizure was 0.02%, with only one documented seizure in one healthy control subject during continuous TBS (Obermann and Pascual-Leone 2009). Therefore, the results of this large review showed that the most common reported adverse events during TBS are comparable to those in conventional rTMS interventions, in terms of both severity and rough incidence (see Rossi et al. 2009). More recently, other studies assessed the safety and tolerability of TBS in children (Krishnan et al. 2015; Hong et al. 2015), in patients with major depression (Bakker et al. 2015), and also in patients with schizophrenia (Tikka et al. 2017). Based on these data, TBS seems to be a safe and efficacious technique, but it must be highlighted that several aspects still need to be evaluated in terms of safety, even in normal subjects, including total pulse number, interval between repeated TBS sessions, intensity of stimulation, and a safe combination of these factors.

4.5.2 Combined rTMS and Transcranial Electrical Stimulation

In recent studies, TMS has been used in combination with other forms of transcranial stimulation based on the simultaneous delivery of weak electric currents on the scalp surface, in order to investigate a potential "priming" effect of TES (both transcranial direct cortical stimulation (tDCS) and transcranial alternating current stimulation (tACS)) on cortical excitability before the application of subsequent rTMS. Theoretically, the interaction between TES and TMS could increase the risk of modifying brain excitability, thereby exposing subjects to a higher risk of seizure or other side effects (Rossi et al. 2009). Studies in which TES was combined with rTMS reported no adverse events during and after the combined interventions (Karabanov et al. 2015; Muller-Dahlhaus and Ziemann 2015), and, similarly, none of the reviewed small clinical studies applying a combination of tDCS and rTMS reported adverse events apart from pain on the scalp in one pilot study (Loo et al. 2009). In summary, currently there is no evidence that the combination of TES and rTMS is unsafe.

4.6 Safety Aspects of TMS Applied in Particular Patient Populations

4.6.1 TMS in Patients with Implanted Brain Electrodes

A lot of TMS studies have been performed in patients with stimulating/recording electrodes implanted both in central and peripheral nervous system, employing mainly single-pulse or paired-pulse TMS and in few cases using rTMS. From the first study (Kofler et al. 1991), three types of electrodes were used in several TMS works in patients with implanted devices: (1) DBS electrodes, (2) epidural electrodes (implanted over the cerebral cortex or spinal cord), or (3) peripheral or cranial nerve stimulating electrodes (e.g., VNS). In some instances the studies were performed in the few days following implantation, while the electrode leads were externalized before connection to a subcutaneous stimulus generator and in other circumstances were performed in patients with the leads connected to implanted stimulators.

Concerning potential safety risk, the application of rTMS in patients with an implanted DBS system could induce significant voltages in the subcutaneous leads in the scalp, which could result in unexpected electric currents in the electrode contacts used for DBS. This can be the case either when the internal pulse generator is turned "on" or "off." The situation may be exacerbated by the coiling of the electrode lead into several loops near the electrode insertion point in the skull (Rossi et al. 2009). Deng and Peterchev (2011) measured ex vivo the TMS-induced voltages and currents in DBS electrodes with the internal pulse generator set in various modes of operation. They showed that voltages as high as 100 V resulting in currents as high as 83 mA can be induced in the DBS leads by a TMS pulse in all modes of the internal pulse generator; these currents are an order of magnitude higher than the normal DBS pulses and could result in tissue damage. When the

internal pulse generator is turned off, electrode currents flow only if the TMS-induced voltage exceeds 5 V.

In summary, based on ex vivo and in vivo studies, it appears that TMS can be safely applied to patients who have implanted stimulators of the central and peripheral nervous system when the TMS coil is not in close proximity to the internal pulse generator. However, detailed information regarding safe distance between the TMS coil and the implanted stimulator, and how coil shape, coil angulation, etc. could influence this relation, is actually missing. Therefore, TMS should only be done in patients with implanted stimulators if there are scientific or medical reasons justifying it, following a prespecified experimental protocol and setting, after approval by the institutional review board or ethics committee.

TMS is considered safe in individuals with VNS systems (Schrader et al. 2005), cardiac pacemakers, and spinal cord stimulators provided that the TMS coil is not activated near the components located in the neck or chest. Additional safety studies should be conducted to evaluate the magnitude of the voltages and currents induced in implanted stimulation systems. Finally, TMS in subjects with cochlear implants should not be performed, due to multiple possibly unsafe interactions between the TMS pulse and the implant.

4.6.2 Navigated TMS for Preoperative Mapping in Neurosurgical Patients

Navigated TMS is a quite novel non-invasive modality for presurgical motor and language mapping in patients with brain lesions in presumed eloquent and perieloquent regions. As it has been demonstrated in multiple studies that nTMS correlates well with intraoperative DES and is likely superior in accuracy to fMRI and MEG (Krings et al. 2001; Picht et al. 2009; Krieg et al. 2012; Tarapore et al. 2012), this technique is becoming a common remarkable step into the standard preoperative workflow for neurosurgical patients with brain lesions. Furthermore, there is increasing evidence that presurgical nTMS improves patient outcomes: patients who have undergone presurgical nTMS mapping receive greater EOR (Frey et al. 2014; Krieg et al. 2014) and have fewer long-term neurological deficits (Krieg et al. 2014, 2015; Sollmann et al. 2015) compared to the patients who have not. Given this increasing application for nTMS and nrTMS, it is of great importance to evaluate if the procedure itself is safe and well tolerated in the neurosurgical population.

The most recent consensus guidelines for application of TMS established in 2009 cover most of the TMS safety aspects in clinical and research settings but do not specifically discuss the risks associated with performing TMS in neurosurgical patients with brain lesions due to the lack of published data on this technique in the neurosurgical population at the time of the meeting date. The nTMS technique has only recently become widely utilized in these patients, and, as more of them undergo nTMS/nrTMS-based mapping procedures, the risk and tolerability of the modality should be described and reported in greater detail. Given that neurosurgical patients are often at greater risk of neurological complications (including seizure), the

application of any neurostimulatory technique must be undertaken with a careful understanding of the risks for the patient.

Very recently, Tarapore et al. (2016) examined the safety and tolerability of nTMS in a large, multicenter cohort of neurosurgical patients. Functional mapping with single-pulse and repetitive nTMS was performed in 733 patients. In this cohort, 57% of patients had left-sided tumors, 50% had frontal tumors, and 50% had seizures secondary to the lesion. Side effects and pain intensity related to the procedure were documented. In this analysis of prospectively collected data aggregated across three institutions and two countries, the authors demonstrated the minimal risk associated with presurgical motor and language mapping using nTMS/nrTMS: over several hundred mapping procedures in patients with intracranial lesions, adverse events—including seizure—were absent. These findings are particularly notable because they are derived exclusively from a neurosurgical population, which arguably has a higher risk of seizure than the healthy population. Although half of these patients had a history of seizures attributable to their lesion, neither single-pulse nor repetitive TMS sequences triggered a seizure in a single patient.

From the results above, it can be stated that preoperative motor and language mapping with nTMS/nrTMS is safe to perform in neurosurgical patients, even in patients with poorly controlled seizures. While further study is necessary, it may be beneficial to remove the restriction on mapping these patients as they may benefit most from having an accurate preoperative map.

4.6.3 TMS in Patients with Epilepsy

As approximately one-third of patients with epilepsy remain with pharmacologically intractable seizures, an emerging therapeutic modality for seizure suppression is rTMS. Open-label studies and case reports demonstrated a reduction of seizure frequency and/or epileptic discharges after rTMS applications (Menkes and Gruenthal 2000; Daniele et al. 2003; Brasil-Neto et al. 2004; Fregni et al. 2005), and two randomized sham-controlled clinical trials of LF rTMS in patients with refractory epilepsy showed a significant decrease in the number of seizures (Misawa et al. 2005; Fregni et al. 2006), while a multicentric placebo-controlled study did not (Cantello et al. 2007). However, well-designed, multiparametric rTMS studies with strict inclusion criteria are needed to increase data consistency and to ascertain reproducibility of these effects.

Because rTMS carries the risk of inducing seizures, among other milder adverse events, its safety in the population with epilepsy should be continuously assessed. As written before, TMS-induced seizures have been observed, both in patients with epilepsy and in healthy volunteers (Anderson et al. 2006; Bae et al. 2007; Rossi et al. 2009). On the other side, there were no TMS-linked seizures among 152 patients with epilepsy who underwent weekly rTMS applications at $\leq$1 Hz in the context of the largest trials designed to investigate the potential of inhibitory LF rTMS to reduce seizure frequency (Theodore 2003; Tergau et al. 2003; Fregni et al. 2006; Cantello et al. 2007; Joo et al. 2007; Santiago-Rodríguez et al. 2008). Bae et al. (2007)

reviewed the safety and tolerability of rTMS applied to patients with epilepsy, which included 30 studies published from 1990 to 2007 and reported a crude per subject seizure risk of 1.4% (95% confidence interval (CI) 0.04–2.82) among 280 subjects: such a low risk in epileptic patients may be due to the use of antiepileptic drugs, which might have a protective effect against TMS-induced seizures.

More recently, Pereira et al. (2016) performed an updated systematic review of the available data in order to further estimate the risk and tolerability of rTMS in epilepsy. They searched the literature for reports of rTMS being applied on patients with epilepsy, with no time or language restrictions, and obtained studies published from January 1990 to August 2015. A total of 46 publications were identified, of which 16 were new studies published after the previous safety review of 2007. The authors found a crude per subject seizure risk of 2.9% (95% CI 1.3–4.5), given that 12 subjects reported seizures out of 410 subjects included in the analysis. Only one of the reported seizures was considered atypical in terms of the clinical characteristics of the patients' baseline seizures. The atypical seizure happened during HF rTMS with maximum stimulator output for speech arrest, clinically arising from the region of stimulation. Although they estimated a larger crude per subject seizure risk compared with the previous safety review, the corresponding CIs contained both risks. Furthermore, the exclusive case of atypical seizure was the same as reported in the previous report. Therefore, the risk of seizure induction in patients with epilepsy undergoing rTMS is small, and the risk of other adverse events is similar to that of rTMS applied to other conditions and to healthy subjects. The similarity between the safety profiles of rTMS applied to the population with epilepsy and to individuals without epilepsy supports further investigation of rTMS as a therapy for seizure suppression. Although the results above indicate a primarily safe risk profile for rTMS in patients with epilepsy, in such instances, for patients with additional risk, rigorous monitoring is still critical: in such instances, the recommendations made in 1998 and in 2009 for EEG monitoring and EMG monitoring from hand/forearm/arm muscles for spread of excitation should be entirely endorsed, along with video recording (if available) of the TMS session to be able to analyze the characteristics of a spell in detail.

4.7 Ethical and Regulatory Questions

The basic ethical and legal requirements, as well as other regulatory and practical issues (where should TMS be done, who should do TMS, neurophysiological monitoring, managing emergencies), are well described in the 2009 safety guidelines, to which reference is made.

An emerging ethical aspect refers to the possibility of inducing an abnormal strengthening of brain activity applying TMS, the so-called neuroenhancement. The latter can be defined as any augmentation of core information processing systems in the brain apart from natural training, including the mechanisms underlying perception, attention, conceptualization, memory, reasoning, and motor performance. Pharmacological neuroenhancement is well recognized in the scientific community, in terms of the use of substances or devices by healthy subjects with the purpose of

cognitive enhancement, e.g., of vigilance, concentration, memory, or mood. TMS, as well as other forms of noninvasive brain stimulation (any TES method), has been proposed for neuroenhancement. Theories behind a potential neuroenhancement include the following mechanisms:

1. *Balance effect*: Balance effects are based on the model of interhemispheric rivalry between homologue areas. Interhemispheric balance effects have been used to account for the paradoxical enhancement of ipsilateral motor function, ipsilateral visuospatial attention, or lateralized verbal memory and language abilities, when using brain stimulation to suppress activity in specific cortical regions.
2. *Entrainment theory*: The entrainment theory is based on the notion that oscillatory activity in brain networks is associated and causally related to specific functions. According to this model, stimulation mimics brain oscillations and has an effect by entraining the brain's natural state.
3. *Stochastic resonance*: Stochastic resonance refers to the notion that injection of subthreshold noise into a system can serve to enhance signal detection.
4. *Net zero-sum framework*: The net zero-sum framework is grounded on the physical principle of conservation of energy in closed systems. Applied to the brain, this model suggests a situation whereby neural "gains" must be matched by neural "losses." Accordingly, if stimulation is able to induce "facilitation," a detrimental opposite effect should occur somewhere else in the brain.

Single-pulse and repetitive TMS studies have claimed an improvement of a given cognitive function following stimulation sessions of a delimited brain area:

1. Dorsolateral prefrontal cortex (DLPFC): attention, risk-taking/impulsivity, and planning and deceptive abilities
2. Inferior frontal cortex (IFC): attention and deceptive abilities
3. Posterior parietal cortex (PPC): attention
4. Primary motor cortex (M1): motor control
5. Temporoparietal junction (TPJ): working memory

This kind of "brain doping" raises numerous ethical and social concerns that should be addressed in future research and safety considerations.

Given these statements, the need of official and recognized approval for the use of TMS appears mandatory. At this regard, in the last decade, several TMS protocols and devices were officially approved in a few countries for specific/therapeutic use: the first endorsement of TMS occurred in 2008 in the United States, where the FDA cleared a device for patients with major depression who have failed one type of medical treatment. Similar approvals were made in Canada, Israel, and Brazil in the following years. Also in the United States, regarding presurgical motor mapping, the FDA approved another device for that specific use. The obtainment of an official endorsement by scientific societies should be the step for those diseases with a satisfactory level of efficacy based on scientific evidence. This step seems mandatory to regulate the clinical/therapeutic use of TMS worldwide.

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Part II

nTMS Motor Mapping

nTMS Motor Mapping: Basic Principles and Clinical Use

5

Dhiego Bastos and Sujit S. Prabhu

5.1 Rationale of Functional Mapping

Gliomas constitute a group of intrinsic brain neoplasms for which no curative therapies currently exist. Cytoreductive surgery remains the cornerstone of glioma treatment, and while surgical resection alone is not sufficient to halt tumor progression, the importance of maximizing the EOR has been increasingly recognized for low-grade (LGG) as well as high-grade gliomas (HGG) (Li et al. 2016; Lacroix et al. 2001; Sanai et al. 2011; Jakola et al. 2012; Coburger et al. 2016). However, preservation of neurological function postoperatively is equally important because it influences patient survival (McGirt et al. 2009). Many tools are available at neurosurgeons' disposal today to help maximize the EOR. The addition of only one modality, such as DTI of the CST preoperatively or intraoperative DES and mapping, can improve the rates of complete resection by 30–40% while preserving neurological function (De Witt Hamer et al. 2012; Wu et al. 2007). Preoperative mapping tools like nTMS can also help to identify eloquent cortical areas and subcortical pathways and better prepare the surgeon to achieve a maximal, safe tumor resection.

Tumors within or close to eloquent motor areas, particularly the precentral gyrus, always involve a challenge between the EOR and the preservation of motor function. It is well known that GTR improves overall survival and progression-free survival in glioma patients (Li et al. 2016; Lacroix et al. 2001). For this reason, although advances in diagnostic imaging have enabled the tumor margins to be more clearly defined, anatomic criteria alone are not always reliable in accurately localizing areas of motor function. Together, anatomical and functional information about the

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cortical and subcortical areas at risk is crucial for avoiding focal neurological deficits during tumor surgery (De Witt Hamer et al. 2012). Intraoperative DES remains the gold standard for motor mapping; however, noninvasive preoperative methods are becoming increasingly accurate and useful to guide surgery, especially for presurgical planning. Such information can not only be used to plan the EOR but also the least invasive trajectory to the tumor, thereby effectively reducing the associated risks of operating in eloquent areas.

5.2 NTMS Motor Mapping in Neurosurgery

5.2.1 General Considerations

The FDA in the United States approved image-guided nTMS (Ref. K091457, November 23, 2009) as a validated device for presurgical functional mapping of the motor cortex. In contrast to other presurgical mapping techniques like fMRI and MEG, which identify cortical areas activated during task execution, nTMS enables the surgeon to determine the eloquent areas that are required for a given function (please also see Chap. 2). In recent years, nTMS has taken a more prominent place in the field of presurgical functional mapping, as a noninvasive approach by mimicking DES by probing and stimulating the cortex transcranially. The integrity of the CST can hence be measured using this technique. Upon coregistration of the patient's MRI scan with predetermined landmarks, a cortical electrical current is induced by applying a transcranial magnetic field to a specific area of the cortex under real-time navigation (please also see Chap. 1) (Picht et al. 2016). This allows the direct activation of the cortex below the area of stimulation, resulting in a corresponding motor response or MEP.

In addition to the accuracy compared to DES, the use of nTMS preoperatively has been correlated with improved patient outcomes, resulting in 16–17% greater rates of GTR and longer progression-free survival of LGG patients of 22.4 versus 15.4 months in the control group (Krieg et al. 2014; Frey et al. 2014; Picht et al. 2016). Finally, low cost and relative ease of use contribute to the increasing use of this modality in preoperative planning.

5.2.2 Methodology and Execution

The full protocol of motor mapping by nTMS is outlined in Chap. 1. The parameters recorded during the nTMS procedure include peeling depth (peeling depth from the scalp surface represents the depth of cortical penetration of the magnetic field), latency, and the amplitude of the rMT. The peeling depth is set on a case-by-case basis to best reveal the cortical anatomy and its relation with the tumor. Surface electrodes are attached to the subject's extremity muscles. The following muscles

are currently recommended for EMG recording in a standard setup, which can then be changed depending on the tumor's location:

Upper extremity:
- APB
- First dorsal interosseus muscle (FDI)
- ADM
- Flexor carpi radialis muscle (FCR)
- Extensor carpi radialis muscle (ECR)
- Biceps brachii muscle (BIC)

Lower extremity:
- TA
- Plantar toe flexor muscle
- Abductor hallucis muscle
- Vastus medialis muscle
- Extensor hallucis longus muscle

Face:
- OrO
- Mentalis muscle (MEN)
- Inferior longitudinal muscle of the tongue

When performing studies on nTMS motor mapping that include intraoperative DES data, it is of utmost importance to use the same muscles for EMG recording for nTMS and DES.

The most important concern that one must have during motor mapping with nTMS is to look for consistency. Proper technique and careful analysis of the hotspots will ensure reliable results. Yet, among patients in whom multiple responses were seen, careful isolation of individuals' legs vs. feet was not achieved.

5.2.3 Analysis

The nTMS technique of cortical mapping is performed by stimulating multiple points on the scalp of the patient corresponding to the possible cortical motor regions and by concomitantly recording MEPs for each stimulation point. The stimulation intensity is usually maintained just above the rMT to limit the neuronal excitation zone and to obtain the greatest functional anatomical accuracy (please also see Chap. 1). To facilitate interpretation, the motor response to each stimulation spot is usually visualized with a color code corresponding to the value of the MEP amplitude. The latency for each MEP has also to be documented and considered during analysis. The resulting nTMS maps generally appear as colored markers corresponding to all of the stimulation spots placed on the individual patient's MRI.

5.2.4 Validation

A comparison of functional areas identified from nTMS mapping to the results of the intraoperative DES demonstrated good accuracy of nTMS in delineating the primary motor cortex, with a reported correlation within 2–6 mm (Tarapore et al. 2012; Krieg et al. 2012).

For nTMS, the patients' cortical representation areas for individual muscles were mapped noninvasively by nTMS before the surgery and compared to locations obtained invasively during surgery by DES of the cortex (Picht et al. 2011). In the study of Picht et al. (2011), the locations where the largest MEPs were elicited from the target muscles (= "hotspots") were mapped with nTMS and DES. It is important to note that nTMS hotspots were not given to the operating surgeon for the DES guidance to guarantee a real-life clinical situation with DES. The operating surgeon and surgery planning team were only informed about the location of motor function around the tumor; they were not part of the team doing the nTMS mapping. After the mappings, DES hotspot coordinates were imported to the original nTMS coordinate system and displayed in the nTMS 3D navigation view to determine the overlap of the DES and nTMS hotspots. The nTMS and DES hotspots were located in the same gyrus in all patients. The mean ± standard error of mean (SEM) distance between the nTMS and DES hotspots was 7.8 ± 1.2 mm for APB (n = 15) and 7.1 ± 0.9 mm for the TA muscle (n = 8). DES mapping was performed under routine operation room conditions under time pressure and clinical demands; therefore, occasionally only a small number of DES stimulations were performed. In such cases, the distance between nTMS and DES hotspots was increased substantially (r = −0.86 for APB). After excluding the cases with fewer than 15 DES APB responses, the mean ± SEM distance between the hotspots was only 4.7 ± 1.1 mm for APB (n = 8).

Subsequent studies in tumor patients like that of Forster et al. (2011) have compared nTMS and fMRI with the intraoperative DES (Forster et al. 2011). The team determined average nTMS-to-DES and fMRI-to-DES distances by comparing distances between DES coordinates and nTMS coordinates and the centroid of fMRI activation coordinates for each muscle. They reported significantly smaller distances (mean ± standard deviation; SD) from nTMS to DES (10.5 ± 5.7 mm) than those from fMRI to DES (15.0 ± 7.6 mm; $p < 0.05$). In their conclusion, the clinical team notes that nTMS is "more precise than fMRI when correlated with intraoperative DES" and nTMS "anticipates information usually only enabled by direct cortical stimulation."

Krieg et al. (2012) compared nTMS and DES by measuring the borders between positive and negative stimulation points on axial slices by using recalibrated screenshots and Brainlab iPlan Net Cranial 3.0.1. They reported a mean distance (mean ± SD) between the borders for nTMS versus DES of 4.4 ± 3.4 mm (range 1.9–9.2 mm). In addition, the investigators evaluated the difference between borders delineating M1 according to BOLD data on fMRI studies and nTMS. With the

9.8 ± 8.5 mm distance (mean ± SD) between nTMS and fMRI (range 5.3–39.7 mm) for the upper extremity and 14.7 ± 12.4 mm (range 8.4–33.5 mm) for the lower extremity, they concluded that nTMS correlates well with intraoperative DES, whereas nTMS and fMRI differed significantly from each other.

Finally, Takahashi et al. (2013) reviewed the six at this time available articles on the correlation of nTMS with DES in patients with Rolandic brain tumors. They reported a mean distance between both methods of 6.18 mm (Takahashi et al. 2013). This value nicely corresponds to the calculated accuracy of the used system (please also see Chap. 1, Table 1).

5.3 Clinical Application

The cortical areas subserving motor function, i.e., not resectable, versus nonfunctional areas, i.e., resectable, are easily determined upon visual inspection of these maps. These functional data merged with the anatomical MRI scans can be transferred to the neuronavigation system used in the operating room to guide surgery and DES, in case the latter is indicated (please also see Chap. 3).

The nTMS-generated hotspots are also used as ROIs to generate DTI tracts for presurgical mapping (Fig. 5.1) (please also see Chap. 6). Intraoperatively, these DTI

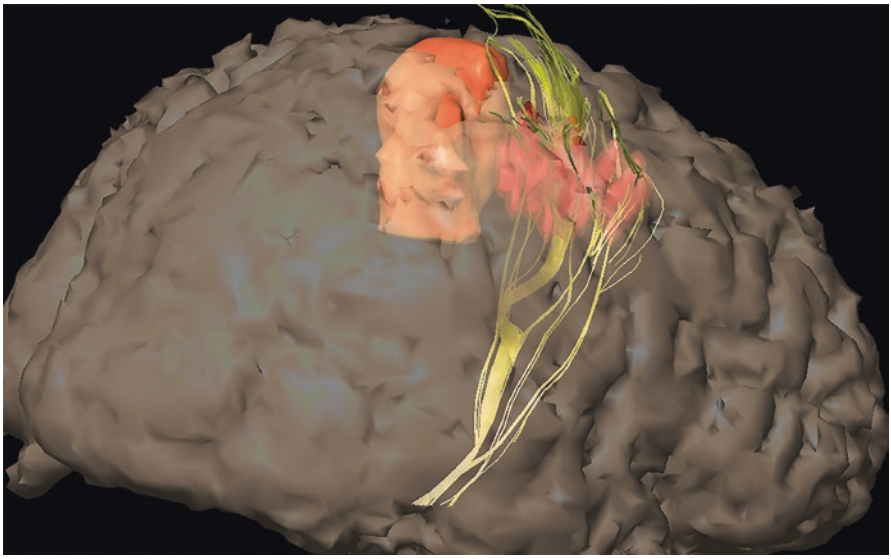

Fig. 5.1 Peritumoral functional anatomy. The nTMS data (*red*) is used to visualize corticospinal fibers (*yellow*) in a metastatic melanoma (*orange*) adjacent to the motor cortex. This clearly improves the identification of the proper peritumoral functional anatomy and also helps our patients to understand the objectives and risks of surgery

tracts can also be used for intraoperative orientation and subcortical mapping, which is increasingly being utilized for motor mapping. The utility of this type of subcortical mapping has been investigated extensively (Prabhu et al. 2011).

As a result of good patient compliance, especially for motor mapping, nTMS has been utilized in longitudinal studies to assess cortical plasticity in patients harboring tumors near the perirolandic area. In one such study, Conway et al. described the utility of assessing cortical plasticity in both HGGs and LGGs using a mathematical model design (Conway et al. 2017).

The risk of discomfort of nTMS motor mapping is minimal to the patient because most of the stimulation points are acquired over the vertex of the head, without any muscle stimulation involved (Tarapore et al. 2016).

The anatomical and functional data provided by preoperative nTMS have shown a very good correlation with those provided by DES performed intraoperatively, with a difference in the location of the motor hotspot that remains less than 15 mm between the two techniques, varying between 4 and 8 mm on average in several studies (Krieg et al. 2012; Paiva et al. 2012; Picht et al. 2009, 2011). Moreover, compared to fMRI, which is widely utilized for identifying the motor cortex, nTMS has better spatial and temporal resolution and provides an immediate result, without recourse to complex postprocessing analysis (please also see Chap. 2). While fMRI relies on neurovascular coupling, nTMS establishes a clearer causal relationship between the stimulation point and observed response (e.g., a MEP). The fMRI signal also depends on the local tumor milieu, including blood flow, edema, and mass effect. While fMRI requires active participation of the individual since it is task-based, nTMS is more of a passive modality and presents fewer restrictions in clinical practice; this is even truer in children. Tarapore et al. also showed a good correlation among the motor map information provided by nTMS, MEG, and DES (Wu et al. 2007). The limitations for the use of MEG include its cost and the time involved in data processing.

More recently, studies have also shown the utility of using nTMS mapping to improve surgical outcomes in patients with tumors adjacent to the motor cortex. These studies have reported modification of the initial surgical strategy in 25–70% of cases, leading to quicker and more extensive resections and favorable long-term outcomes related to EOR in patients who have had preoperative nTMS mapping, compared to the control group, in which no nTMS mapping was performed (Krieg et al. 2012; Picht et al. 2012, 2013, 2016; Rizzo et al. 2014).

Intraoperative mapping of the lower extremity is challenging for anatomical reasons, as the foot/leg motor homunculus is in close proximity to the superior sagittal sinus along the interhemispheric fissure, making its localization difficult to confirm by intraoperative DES. Also, there is no sulcus between the foot/leg motor homunculus and the supplementary motor area (SMA), making the distinction between the two areas difficult to determine on routine MRI (Fisicaro et al. 2015). Therefore, mapping in the preoperative setting is important for planning surgical intervention. In our recent series of 21 patients, nTMS had good sensitivity to provide

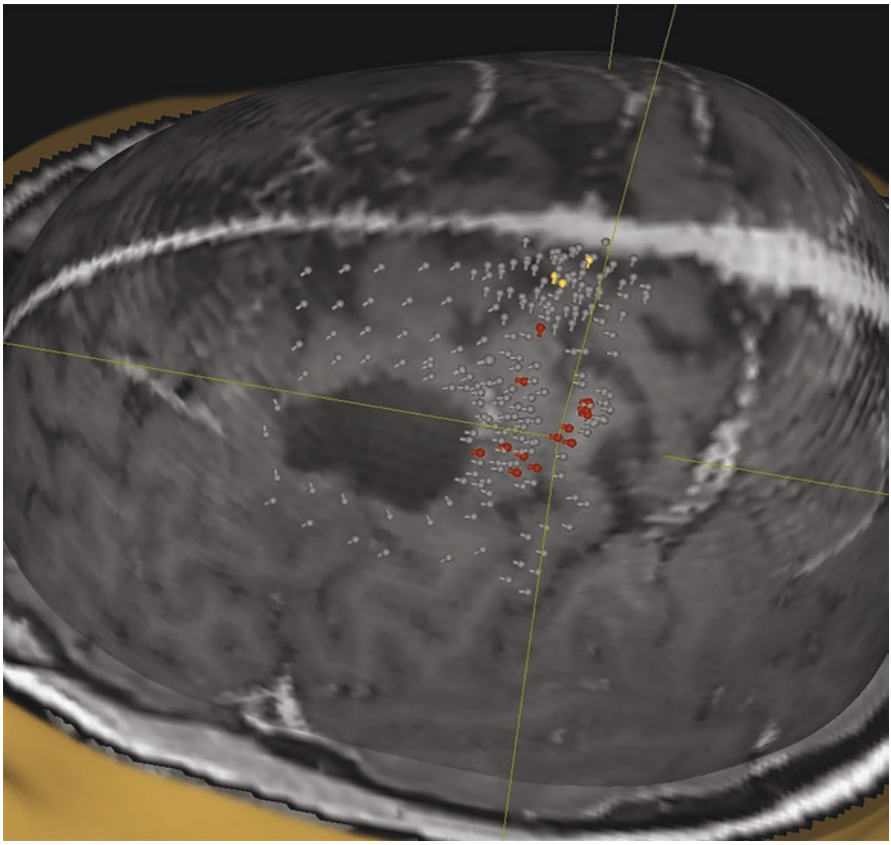

Fig. 5.2 Intraoperative DES guidance. This patient had a previous LGG resection in the right premotor cortex (PMC). The nTMS data show positive spots in *yellow kegs* in the leg area and *red kegs* showing the hand area. Both of these areas were stimulated and confirmed during intraoperative cortical DES mapping

preoperative functional information prior to surgical resection for tumors in close proximity to the lower extremity motor areas (Fig. 5.2) (unpublished data).

5.4 Conclusion

In summary, nTMS for cortical mapping of motor areas is a very robust tool to identify and preserve motor function. The information obtained can be applied to both surgical preplanning and intraoperative orientation to minimize neurological injury and for safe maximal resection of tumors within or adjacent to motor areas of the brain.

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nTMS-Based DTI Fiber Tracking of Motor Pathways

6

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6.1 Introduction

The nTMS technique is able to provide reliable mapping of the functional organization of the primary motor cortex, helping neurosurgeons to plan the best customized strategy to preserve it during surgery (Frey et al. 2014; Picht et al. 2009; Takahashi et al. 2013; Krieg et al. 2012b, 2013, 2014). Indeed, postoperative motor deficits are more often the result of an injury to the descending motor pathway during surgery than to the motor cortex. The subcortical functional anatomy has been difficult to interpret until the introduction of DTI FT (Basser et al. 1994). This technique provides a time-efficient, noninvasive, qualitative, and quantitative method to study brain connections (Catani et al. 2002; Catani and Thiebaut de Schotten 2008) that represents a valid in vivo alternative to classic fiber dissection studies in cadaver labs. In fact, although operator-dependent, prone to several artifacts, and having low-resolution and persistent technical limitations, DTI FT can be repeatedly applied in large populations and correlated with behavioral and other functional measures (Basser 1995; Goebell et al. 2006; Minati et al. 2007; Sarubbo et al. 2015; Hakulinen et al. 2012).

Here, we describe the technique and data for a somatotopic DTI FT of the CST based on somatotopic nTMS mapping of the motor cortex. We also analyzed the accuracy of this technique in comparison to the standard anatomical DTI FT technique. The reliability of both approaches was also assessed via comparison to intraoperative subcortical DES. For the sake of readability of this chapter, fibers

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originating from the cortical face motor area are also named CST fibers instead of the anatomically correct term "corticobulbar fibers."

6.2 Rationale Behind nTMS-Based Tractography

Due to its peculiarities, several authors have widely studied the CST, and numerous studies on both physiological characteristics and pathological alterations have been published to date (Pujol et al. 2015; Romano et al. 2011; Giordano et al. 2015; Morita et al. 2011). Some of these have confirmed and clarified previously known data obtained using nonimaging methods, and others have added substantial information that, although still to be confirmed, is an important advance in anatomical knowledge. A significant number of publications have appeared in the last decade in which fiber streamlines extracted with DTI FT and indicated as the CST do not completely respect the classical course of this tract, thus making the data obtained potentially incorrect and not reproducible (Pujol et al. 2015; Kristo et al. 2013; Wakana et al. 2007).

Frequent examples of the latter are the presence of streamlines leaving the main bundle of the tract and joining the corpus callosum, either crossing the midline at the level of the pons (the only decussation of the CST is at the medullary level) or, finally, joining the superior and middle cerebellar peduncles (representing mostly fibers of the extrapyramidal system). Some authors deliberately chose to represent only the portion of CST originating from the precentral gyrus, whereas others showed the full extent of it, including its premotor and postcentral portions. This has important consequences for both data interpretation and the comparison of results from different studies that require thorough knowledge of the role of each separate component of the CST.

The main drawback of DTI FT is the choice of anatomical landmarks for the computation of the CST. Several papers reported the use of different seeding ROIs for the DTI computation of the CST, including M1, internal capsule (IC), and cerebral peduncle (Kwon et al. 2011; Weiss et al. 2015; Niu et al. 2016; Catani and Thiebaut de Schotten 2008; Catani et al. 2002; Holodny et al. 2005). The choice of different anatomical landmarks as seeding ROIs and/or ROI malpositioning makes DTI FT of the CST an operator-dependent technique, thus reducing its reliability and reproducibility (Niu et al. 2016). Moreover, it has been widely demonstrated that anatomical landmarks do not necessarily correspond to the functional organization of neural networks, including the motor pathway. This is particularly evident in brain tumor patients, in which the presence of the tumor itself can lead to plastic reorganization of the motor network, especially at a cortical level, causing a mismatch between anatomical landmarks and functional pathways (Takahashi et al. 2012; Niu et al. 2016). This is one major cause of the abovementioned incongruence in the representation of the CST by using the classic anatomical-based DTI FT. Such an issue can be overcome by combining the classic DTI FT technique with

functional neuroimaging, improving the reconstruction of the CST. The nTMS approach represents the most accurate technique to provide a preoperative functional characterization of the motor cortex, being more reliable than fMRI and correlating with IOM findings (Picht et al. 2011a; Takahashi et al. 2013; Krieg et al. 2012b).

Few studies have described the use of the nTMS maps of the motor cortex as a seeding region for the DTI FT. The use of the nTMS-based DTI FT improves the visualization of the CST in brain tumor patients, in which anatomical distortion caused by mass effect and neuroplasticity phenomena induced by tumors reduces the reliability of standard DTI FT results (Conti et al. 2014; Krieg et al. 2012a; Frey et al. 2012; Forster et al. 2015; Weiss et al. 2015).

Moreover, nTMS allows interpretation of the somatotopic organization of the motor cortex, distinguishing between the cortical representation of face, arm, and leg muscles. These functional data can be successfully used as a seeding region to obtain a functional characterization of the CST through the nTMS-based DTI FT (Conti et al. 2014).

6.3 Technical Aspects of the Approach

6.3.1 Patients

We prospectively collected data on patients operated on for space-occupying supratentorial lesions (tumors and cavernous angiomas) located in or around the motor pathway at the Department of Neurosurgery of the University of Messina, Italy, between January 2014 and January 2016. In the study, we included adult patients affected by intra-axial brain lesions located superficially and/or deeply within a distance of 10 mm from the motor cortex and/or CST. Exclusion criteria were age <18 years old and any contraindication to undergoing an MRI scan and/or nTMS mapping (pacemaker, cochlear implants, non-MRI compatible prosthesis, etc.). All patients signed a written informed consent for the aim of the publication of clinical data according to the IRB at our institution.

6.3.2 Preoperative MRI

All patients underwent a preoperative brain MRI scan using a 3T scanner (Achieva 3T, Philips Medical Systems, the Netherlands). T1-weighted, gadolinium-enhanced multiplanar reconstruction (MPR) (FS = 3, repetition time = 8.1, echo time = 3.7); 3D fluid attenuated inversion recovery-volumetric isotropic T2w acquisition (FLAIR-VISTA) (FS = 3, repetition time = 8000, echo time = 331.5/7); and diffusion-weighted imaging (DWI with 32 directions or gradients and 80 slices for each direction; FS = 3, repetition time = 2383.9, echo time = 51.9) for DTI computation were obtained.

6.3.3 nTMS Mapping of the Motor Cortex

Preoperative mapping of the motor cortex was performed using the Nexstim eXimia NBS system 4.3 (Nexstim Plc, Helsinki, Finland). The direct correspondence between the stimulated spot on the motor cortex and the recorded MEP is able to provide a somatotopic representation of the motor area (please also see Chap. 1). The mapping was performed within 48 h before the scheduled surgery. Patients were seated in a comfortable reclining chair. The patients' heads and the anatomical reference exam (a volumetric contrast-enhanced T1-weighted dataset or FLAIR sequence in cases of non-contrast-enhancing lesions) were coregistered using anatomical landmarks and surface registration (Picht et al. 2009; Krieg et al. 2012b).

Stimulation was performed using a standard navigated figure-of-eight coil. The first step consists of the determination of the rMT for the FDI in the hemisphere ipsilateral to the lesion. Motor cortex mapping was performed with a stimulation output of 110% of the rMT, increasing the intensity to up to 130% of the rMT for lower limb mapping. All MEPs with amplitude >50 μV (peak-to-peak) were considered motor-positive responses. MEPs were recorded using standard electromyography electrodes (Neuroline 720; Ambu, Ballerup, Denmark) from three channels, choosing at least one muscle for each body segment (face, arm, or leg) to obtain the somatotopic organization of the motor cortex. The muscles usually used were the FDI, APB, ECR, BIC, TA, MEN, and OrO. The choice depended on the tumor location and the patient's motor performance. The mean time needed for the nTMS mapping was 45 min.

Only patients in whom we were able to simultaneously obtain an nTMS somatotopic map of the motor areas of the face, arm, and leg were enrolled in the study. At the end of the procedure, the nTMS map of the motor cortex was exported in a DICOM format and subsequently imported into the neuronavigation system for coregistration with the DWI images and DTI FT computation.

6.3.4 Image Fusion and DTI FT of the CST

Further technical aspects of DTI itself as well as nTMS-based DTI FT are provided in Chap. 9 (Sect. 9.3).

From a practical point, the DWI sequences were imported together with the nTMS map of the motor cortex and the anatomical reference MRI exam (contrast-enhanced T1-weighted or FLAIR sequences) into a neuronavigation system (StealthStation® S7, Medtronic Navigation, Coal Creek Circle Louisville, CO, USA). The complete workflow for DTI FT, including tensor computation, ROI selection, as well as standard and nTMS-based fiber tracking, was performed on the StealthStation® S7 system using the StealthViz® software (Medtronic Navigation, Coal Creek Circle, Louisville, CO, USA). DWI images were coregistered with the reference anatomical exam and the nTMS map and then used to compute the DTI tensor. Once the tensor was calculated, the software created the apparent diffusion coefficient (ADC) map and the directionally encoded color (DEC) map. The DEC

map was therefore used to choose the ROIs for the CST tracking in the hemisphere affected by the space-occupying lesion. A multiple-ROI technique was used for the somatotopic DTI FT. The first ROI was placed at the anterolateral portion of the ipsilateral cerebral peduncle (Fig. 6.1a). The nTMS map of the motor cortex was selected as the second ROI. It was divided into three different areas corresponding to the cortical motor representation of muscles of the three different body segments (face, arm, and leg), to track the CST with its somatotopic organization. Each area corresponded to a segmentation area, including all of the positive spots the nTMS provided for each somatotopic area (face, arm, and leg). This was done according to the different muscular responses recorded during stimulation and individually selected as the second ROI. For each patient, we obtained at least three ROIs, corresponding respectively to the somatotopic representation of the contralateral face (MEN muscle), arm (ECR and/or FDI and/or BIC muscles), and leg (TA muscle) (Fig. 6.1b). Then, we separately computed the DTI tractography of each functionally different CST fiber bundle using the anterolateral portion of the ipsilateral cerebral peduncle as the first ROI and each somatotopically different motor cortex areas as the second ROI (Fig. 6.1c).

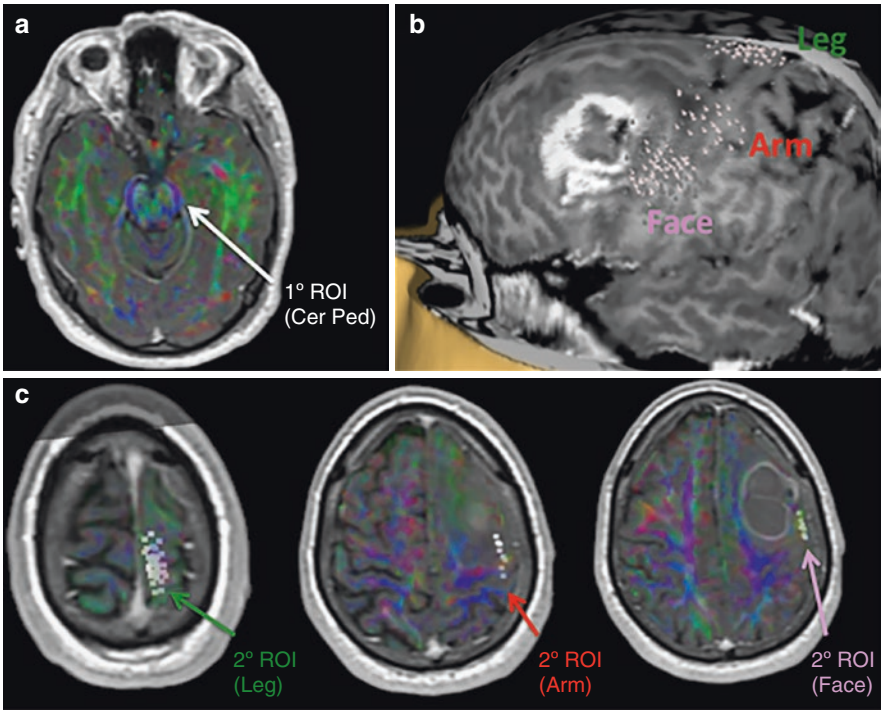

Fig. 6.1 nTMS-based DTI FT of the CST in the case of a left frontal glioblastoma. (**a**) The DEC map was coregistered with a reference MRI scan to select the first ROI corresponding to the anterolateral portion of the cerebral peduncle; (**b**) the somatotopic nTMS map of the motor cortex is divided into three ROIs, each corresponding to the cortical representation of leg, arm, and face muscles; (**c**) the three nTMS-based functional areas are separately used as second ROIs to compute three different components of the CST

The DTI FT was performed through a deterministic approach using the fiber assignment by continuous tracking (FACT) algorithm with the following parameters:

- Fractional anisotropy (FA) = 0.20
- Vector step length = 1 mm
- MFL = 20 mm
- Seed density = 3.0; maximal directional change = 45°

For the nTMS-based DTI FT, the maximal directional change was 45° for arm and leg fibers and ranged from 75°–90° for face fibers. To visualize face motor fibers, directional change was increased progressively until the bundle could be identified. Both standard and nTMS-based DTI FT were performed using the same computation parameters, except for angulation.

The simultaneous visualization of different fiber bundles obtained through the nTMS-based DTI FT represented the entire CST, reflecting its functional organization (Fig. 6.2). This strategy allowed for including only those motor fibers in the

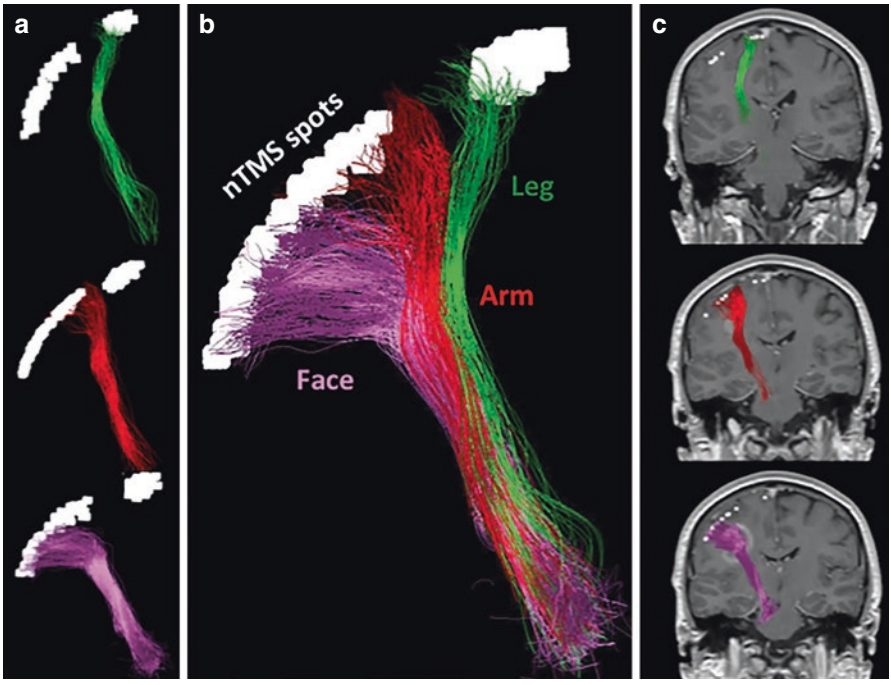

Fig. 6.2 3D reconstruction of an nTMS-based somatotopic DTI FT of the CST. (**a**) 3D reconstruction of each functionally different fiber bundle (leg = *green*, arm = *red*, face = *purple*) forming the CST with the corresponding nTMS map (*white spots*); (**b**) coronal view of the whole somatotopic 3D reconstruction of the CST; (**c**) navigable tractography after coregistration with a reference anatomic MRI examination

CST computation, which originated from the motor cortex objectively localized by the nTMS system. Thus, real functional mapping of the motor pathway was used pre- and intraoperatively for presurgical planning and as a guide for lesion resection.

After surgery, standard DTI FT of the CST through a single-ROI technique placed on classic anatomical landmarks was performed. According to the literature, the seeding ROI was located in correspondence with the anterolateral portion of the ipsilateral cerebral peduncle and was the same in size and location as that used for the nTMS-based reconstruction.

6.3.5 Intraoperative Verification of the Accuracy of the nTMS-Based DTI FT of the CST

The nTMS-based DTI FT of the CST was used during surgery as a guide for subcortical stimulation in all patients. Subcortical DES was performed by monopolar stimulation through the NIM-Eclipse system (Medtronic, Minneapolis, MN, USA). Subdermal needle electrodes were placed to record MEPs in correspondence with the same muscles used in each patient during the nTMS motor mapping. Monopolar stimulation (trains of 3–4 stimuli for cranial surgery, pulse duration of 50–500 μs, inter-stimuli interval (ISI) of 2–4 ms (250–500 Hz)) was performed with an increasing intensity to obtain a motor response with an upper limit of 25 mA. Close to the CST, in tumor cases, resection was performed layer by layer, in which each layer was followed by subcortical stimulation. To avoid damage to the CST, we continued with the lesion resection guided by the subcortical DES until we obtained an MEP at a stimulation intensity of 5 mA. In general, when an MEP was obtained at this stimulation intensity, the tumor resection was discontinued. These stimulation points were stored in the neuronavigation system and used to measure the distance between the stimulation site and the CST, as it was computed using both DTI FT techniques (standard and nTMS-based). We exported the coordinates of each subcortical DES point and reported them on the preoperative MRI scan, which was coregistered to the CST computed by the two different DTI FT techniques. The distance between the stimulated subcortical DES point and the CST computed by the two DTI FT techniques was measured and stored together with the used subcortical DES intensity.

At this point, a correlation analysis between distance and subcortical DES intensity was performed to assess the reliability and eventual differences of the two DTI FT reconstructions.

Moreover, we analyzed the correspondence with the muscular response evoked by subcortical DES and the somatotopic organization of the CST provided by the nTMS-based DTI FT to verify the concordance between the activated muscle (i.e., MEN, FDI, TA) and the nearest functionally different CST fiber bundle (i.e., face, arm, leg).

6.4 Results

Thirty-five patients (19 males, 16 females, mean age of 54 ± 14.3 years old, range of 19–76 years, operated on between January 2014 and January 2016) were included in the study. Approximately 150–200 stimulations were necessary to obtain a satisfactory somatotopic representation of leg, arm, and face muscles in each patient. All patients tolerated the procedure well.

The nTMS-based DTI FT of the CST was performed the day before surgery, whereas the standard DTI FT was obtained after surgery using the same imaging datasets for each patient. In all cases, the CST fiber tracking using the two different techniques was successfully obtained.

The nTMS-based reconstruction allowed the visualization of the somatotopic organization of the CST in all cases (Fig. 6.3). We differentiated fiber bundles of the arm, leg, and face fibers using a color-coded technique (green for leg fibers, red for arm, and purple for face). Such a somatotopic reconstruction provided helpful anatomical and functional information about the morphofunctional organization of the entire motor pathway. This allowed the surgeon to have a more accurate awareness of the surgical risks, being able to preoperatively analyze the spatial relationship

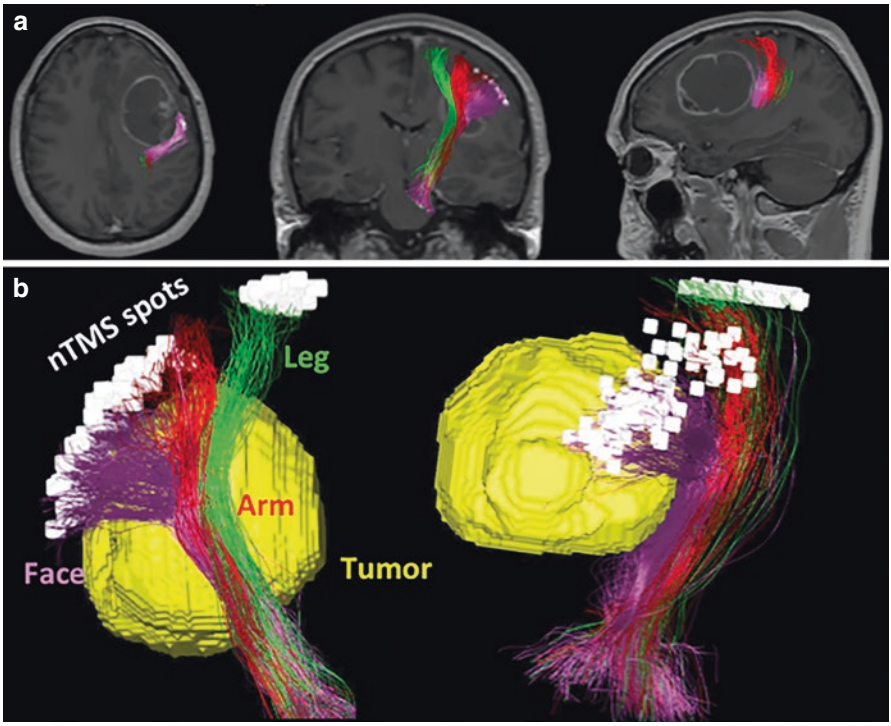

Fig. 6.3 Coregistration of the nTMS-based DTI FT of the CST in the case of a left frontal GBM. (**a**) Coregistration of the nTMS-based DTI FT of the CST (leg fibers = *green*; arm fibers = *red*; *purple fibers* = face) with the reference T1-weighted anatomic examination; (**b**) 3D reconstruction of the CST and its spatial relationship to the tumor (*yellow*). The tumor is located just posteriorly to the CST and involves face fibers (*purple*)

between the lesion and the functionally different CST fiber bundles and use all of this morphofunctional information intraoperatively as a guide for lesion resection.

6.4.1 Intraoperative Analysis of Accuracy of nTMS-Based DTI FT of the CST

Subcortical DES was used to guide a safe lesion resection and assess the reliability and accuracy of the nTMS-based DTI FT of the CST. In tumor cases and if preoperatively planned, the resection was stopped when we obtained an MEP with a DES intensity of 5 mA. The distance between the last stimulation point and the CST as displayed by the nTMS-based DTI FT was 4.64 ± 0.78 mm (mean ± SD; Fig. 6.4a). In general, we observed a concordance between the type of recorded MEP and the functionally different CST fiber bundles obtained using the nTMS-based technique in all cases. We recorded the specific MEP (arm, face, or leg) that we expected according to the nTMS-based CST reconstruction (Fig. 6.4a–c).

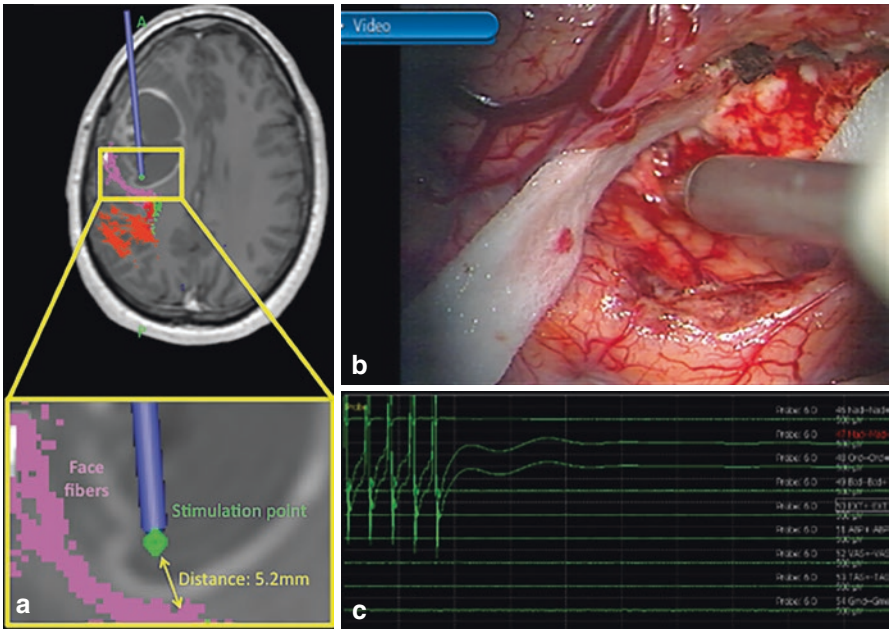

Fig. 6.4 Subcortical DES confirms the spatial accuracy of the CST. Subcortical DES confirmed the spatial accuracy of the CST and its somatotopic organization, as delineated by nTMS-based DTI FT. (**a**) Intraoperative navigation during removal of a left frontal GBM. The somatotopic organization of the CST is represented by different colors of fibers (*green* = leg; *red* = arm; *purple* = face). The *blue stylet* represents the navigated probe used for subcortical DES. The *green point* at the end of the stick represents the subcortical DES point that evoked a MEP using a 6-mA stimulation intensity; (**b**) the corresponding microscope view during tumor resection; (**c**) subcortical DES recording showing correspondence between the muscles activated by subcortical DES and somatotopic CST organization, as displayed by functional tractography. The responses were evoked at the right masseter and OrO muscles and corresponded to the CST face fibers (*purple*). The distance between the stimulation point and the CST, as displayed by the neuronavigation system, was 5.2 mm

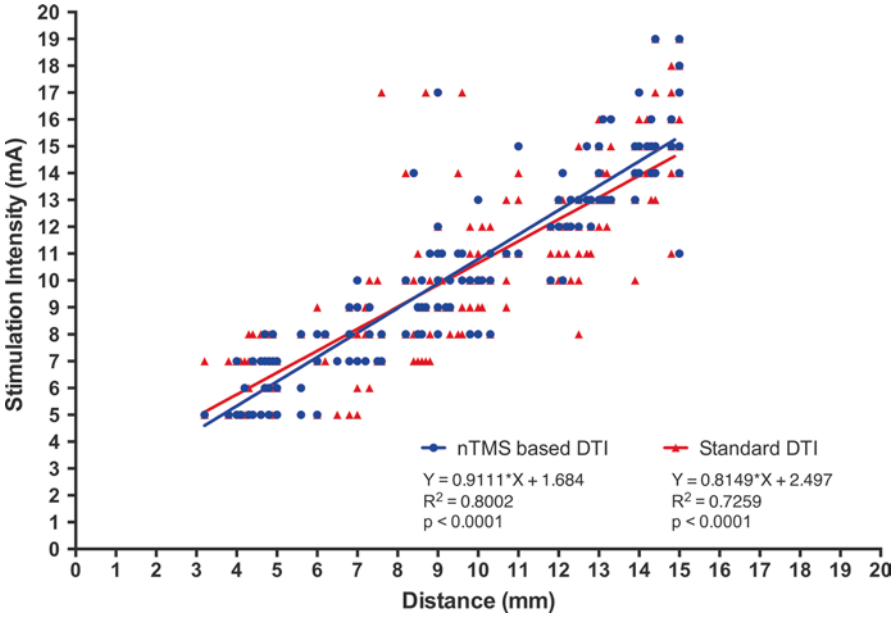

Fig. 6.5 Linear regression analysis between distance to the CST and subcortical DES intensity. Linear regression analysis showing the correlation between the distance from the CST (mm) and the intensity of the subcortical DES (mA) at each stimulated point for both techniques. We found a positive linear correlation, as described by the equation $y = 0.9111x + 1.684$ for the nTMS-based technique (*blue*) and by the equation $y = 0.8149x + 2.497$ for standard tractography (*red*). The correlation with the linear model was stronger for the nTMS-based technique ($R = 0.95$ vs. 0.93; $R^2 = 0.8002$ vs. 0.72597). Note the different slopes and y intercepts of the two linear models, suggesting different reliabilities between the two techniques ($p = 0.02$)

6.4.2 Analysis of Correlation Between CST Distance and Subcortical DES Intensity

After surgery, the two DTI FT techniques were compared through a correlation analysis between the distance from the CST and the intensity of the subcortical DES points. We retrieved a total of 242 stimulation points from the neuronavigation system. The mean distance from the CST was 9.2 ± 0.4 mm (mean ± SD) for the nTMS technique. Statistical analysis showed a positive correlation between the CST distance and the subcortical DES intensity ($R = 0.95$; $p < 0.0001$). Regression analysis showed a linear correlation expressed by the equation $y = 0.9111x + 1.684$. Fitting with the linear model was stronger as compared to standard DTI FT ($R^2 = 0.8002$ vs. $R^2 = 0.7259$, with a significantly different slope, $p = 0.02$) (Fig. 6.5).

6.5 Discussion, Limitations, and Other Approaches

The nTMS-based DTI FT is a reliable technique that can provide an increased preoperative awareness for the spatial relationship between the space-occupying lesion and the entire motor pathway, improving the evaluation of risks related to surgical

treatment. The major advantage as compared to the standard DTI FT is the reconstruction of the CST based on objective neurophysiological findings obtained through nTMS mapping and the ability to visualize its somatotopic organization.

Standard DTI FT is affected by several pitfalls, especially because it is an operator-dependent technique. Final reconstruction can be influenced by several factors, including the choice of anatomical landmarks as seeding ROIs, use of different reconstruction algorithms and software, and presence of peritumoral edema (Feigl et al. 2014; Duffau 2014; Weiss et al. 2015; Lu et al. 2003).

Anatomical landmarks for DTI reconstruction of the CST are well defined in the literature (Catani et al. 2002; Catani and Thiebaut de Schotten 2008; Conturo et al. 1999). Nevertheless, it is well known that the presence of space-occupying lesions, especially if slow-growing, can induce neuroplasticity phenomena or a simple derangement of anatomical structures that can make the placement of seeding ROIs much more difficult (Yen et al. 2009; Takahashi et al. 2012; Niu et al. 2016; Lehericy et al. 2000; Robles et al. 2008).

The use of nTMS-based DTI FT reduces this limitation, as it is based on objective neurophysiological muscular responses, thus taking into account the eventual reorganization of the motor cortex due to neuroplasticity induced by the lesion. This also increases the reproducibility of CST reconstructions compared to the standard technique, increasing the agreement between operators.

The use of functional cortical nTMS data as a seeding region for DTI FT has been described in few recent studies (Frey et al. 2012; Krieg et al. 2012a; Weiss et al. 2015; Forster et al. 2015). Moreover, another advantage of using nTMS is the possibility of mapping the cortical representation of face muscles (Weiss et al. 2013). This provides the somatotopic organization of the motor cortex that can be successfully used to improve the visualization of the CST (Conti et al. 2014). In particular, another limitation of standard deterministic DTI FT is the low ability to visualize the most lateral CST fiber bundles that bend to connect to the cortical representation of face muscles (Burgel et al. 2009; Lee et al. 2015). The use of somatotopic nTMS maps including the representation of face muscles allows visualization of the most lateral components of the CST and increases its reliability.

The nTMS-based DTI FT reconstruction correlated well with DES findings and was more accurate compared to the standard DTI FT. In particular, we observed a correspondence between the type of recorded MEP (arm, leg, or face muscles) and the type of the stimulated CST fiber bundle, as it was visualized with its somatotopic characterization by the neuronavigation system. Moreover, the correlation between the distance from the nearest CST fiber bundle and intensity of subcortical DES responses was shown to be stronger for the nTMS-based DTI FT compared to the standard technique.

All of these data suggest that the nTMS-based strategy is reliable and accurate and can be successfully used for preoperative planning for space-occupying lesions located in or near the motor pathways. The nTMS-based DTI FT increases the awareness of the spatial relationship between the CST and the suspected motor-eloquent lesions, especially if deep-seated. In the latter case, its use could also modify surgical indications thanks to an improved preoperative risk/benefit analysis of surgical treatment.

Moreover, the nTMS-based reconstruction of the CST can be successfully used during surgery as a further support for IOM and lesion resection. The combination of functional CST tractography and subcortical DES helps the surgeon to respect the planned operative strategy by guiding subcortical DES. In the present series, tumor resection was performed layer by layer, repeating the stimulation along with the resection of layers of tumor. The CST was accurately localized by nTMS-based DTI FT, and MEPs were evoked by progressively decreasing current intensities along with tumor resection. Resection was then interrupted when the MEP was evoked by low-intensity stimulation (5 mA), indicating proximity of the CST. The mean distance from the CST was, at this point, 4.64 ± 0.78 mm (mean ± SD). Analysis of the correlation between stimulation intensity and distance from the CST showed a strong linear positive correlation ($R = 0.95$; $R^2 = 0.8002$).

Actually, five studies performed a quantitative analysis of the relationship between the distance from CST and stimulation intensity, providing varying results (Nossek et al. 2011; Ostry et al. 2013; Maesawa et al. 2010; Ohue et al. 2012; Kamada et al. 2009). Four of these studies found a linear correlation between the distance and the stimulation intensity (Ostry et al. 2013; Nossek et al. 2011; Ohue et al. 2012; Maesawa et al. 2010), whereas in one study, a nonlinear relationship was found (Kamada et al. 2009). Furthermore, equations expressing such a correlation were remarkably different. Ohue et al. found a relation described by the equation $y = 0.972x + 0.120$ with a slope of 0.972 (close to 1) and a y intercept of 0.120 (close to 0) using postoperative tractography (Ohue et al. 2012). This is a quasi-ideal correlation with 1 mA corresponding to 1 mm from the CST. Our findings demonstrated a linear correlation with a good slope value (0.9111), but a relatively high y intercept value (1.684), meaning a closer distance for each mA. This can be explained by the brain shift due to the use of preoperative imaging. Nevertheless, the correlation and the fitting with the linear model was stronger for the nTMS-based DTI FT, indicating a significant higher accuracy as compared to standard DTI FT ($p = 0.02$).

We also found that the type of MEPs elicited (face, arm, or leg) was concordant with the nearest functionally different fiber bundle, as displayed by the somatotopic tractography. This serves as a further confirmation that the functional nTMS-based technique was accurate.

6.5.1 Alternative Protocols for nTMS-Based DTI FT

To date, six articles have already reported different protocols for nTMS-based DTI FT of the CST (Conti et al. 2014; Frey et al. 2012; Krieg et al. 2012a; Forster et al. 2015; Weiss et al. 2015). Evidence from the literature suggests that the number of directions used for DTI acquisition can influence FT results. In particular, the higher the number of directions, the more reliable the reconstruction of tracts, six being the minimum number of gradients needed to compute the tensor (Yao et al. 2015; Lebel et al. 2012; Basser et al. 1994). In the published studies, nTMS-based DTI FT has been always computed using ≥20 directions (Conti et al. 2014; Weiss et al. 2015;

Frey et al. 2012; Forster et al. 2015), except in one study (Krieg et al. 2012a). Reported DTI tracking parameters are quite variable, the following being the most common:

- Vector step length = 1.6 mm (Frey et al. 2012; Weiss et al. 2015).
- MFL ≥100 mm (Frey et al. 2012; Krieg et al. 2012a; Conti et al. 2014; Weiss et al. 2015).
- Angulation threshold = 30° (Frey et al. 2012; Krieg et al. 2012a; Weiss et al. 2015), even if it can be increased to 45° to visualize the most lateral component of the CST (face fibers) (Conti et al. 2014).

More attention must be paid choosing the best FA value to stop tracking; an attempt to standardize the used FA stop value has been proposed by using a value corresponding to the 75% of the individual FA threshold (the lowest FA value at which a single CST fiber is visible) (Frey et al. 2012). Nevertheless, customized values need to be selected in each case according to peritumoral edema, balancing the necessity of identifying the CST and the danger of visualizing aberrant fibers (higher risk for low FA values). Lastly, a two-ROI technique for seeding was used in all studies. The first ROI is commonly placed at the brainstem (anterior pons/cerebral peduncle), providing more accurate results than using the IC (Weiss et al. 2015). The second ROI is usually placed over an area including all of the nTMS-positive spots and converted to a volume representing the entire M1 (Frey et al. 2012; Krieg et al. 2012a). The somatotopic reconstruction of the CST can be obtained by drawing separate seeding areas corresponding to the somatotopic organization of the motor cortex (foot, hand, and face areas) and using each area as a second seeding ROI (Conti et al. 2014; Forster et al. 2015). Alternatively, the hotspots of different somatotopic areas can be enlarged to 2–3 mm and separately used as a second seeding ROI for the somatotopic FT of the CST (Weiss et al. 2015). Table 6.1 summarizes the different nTMS-based DTI FT protocols currently reported in the literature.

6.5.2 Limitations of DTI FT

Nevertheless, some DTI FT limitations cannot be avoided even if using the nTMS-based strategy. First of all, the presence of excessive perilesional edema seriously hampers the optimal computation of the water diffusion tensor, especially in the voxels nearest to the lesion (Lu et al. 2003; Yen et al. 2009). Despite the fact that the use of specific second ROIs in the nTMS map represents a valid method to ensure that the software computes fibers, the presence of edema dramatically reduces the values of anisotropy needed to obtain a reliable calculation of the tensor, thus hampering the visualization of reliable fibers. In this scenario, the only way to visualize CST fibers is to use low FA values for DTI computation, resulting in the visualization of aberrant fibers and reducing the accuracy of DTI FT, regardless of the use of the standard or nTMS-based strategy.

Table 6.1 Different published protocols for the nTMS-based DTI FT of the CST

Study	DTI acquisition	DTI FT parameters				Seeding ROIs		Software
		Vector step length	MFL	Angulation threshold	FA value	1st ROI	2nd ROI	
Frey et al. (2012)	24 direction (*b* value = 1000 s/mm^2)	1.6 mm	110 mm	30°	75% of FA threshold	Brainstem/IC	All nTMS positive spots (each enlarged by 6 mm)	Brainlab iPlan 2.0
Krieg et al. (2012a)	6 directions (*b* value = 800 s/mm^2)	/	100 mm	30°	Variable (<0.20)	Brainstem (at the level of the tentorium)	All nTMS positive spots (each enlarged by 2 mm)	Brainlab iPlan 3.0.1
Conti et al. (2014)	32 direction (*b* value = 1000 s/mm^2)	1 mm	110 mm	45°	0.20	Brainstem (cerebral peduncle)	All nTMS positive spots (distinguishing between leg, arm and face spots)	Medtronic StealthViz—StealthStation S7
Weiss et al. (2015)	30 direction (*b* value = 800 s/mm^2)	1.6 mm	1 mm (plausibility cut-off = 121.5 mm)	30°	100% FA threshold (plausibility cut-off = 0.105)	Brainstem (anterior pons)/ IC (posterior limb)	nTMS hotspots for foot, hand and tongue muscles (each enlarged by 2–3 mm)	Brainlab iPlan 3.0.0
Forster et al. (2015)	20 direction (*b* value = 700 s/mm^2)	/	80 mm	/	0.20	Brainstem (ventral pons/ cerebral peduncle)	All nTMS positive spots (distinguishing between leg and hand spots)	Brainlab iPlan 3.0.3
Weiss et al. (2015)	30 direction (*b* value = 800 s/mm^2)	1.6 mm	1 mm	30°	100% FA threshold	Brainstem (anterior pons)	nTMS hotspots for foot, hand and tongue muscles (each enlarged by 2–3 mm)	Brainlab iPlan 3.0.0

This table provides an overview on the currently published protocols for nTMS-based DTI FT

Moreover, in patients with severe preoperative motor impairment, nTMS could not elicit any motor response due to tumor infiltration of the motor cortex/CST, and therefore, it cannot be used as a seeding region for DTI FT of the CST. Nevertheless, some reports have been published describing the possibility of obtaining an nTMS mapping of the motor cortex, even in hemiplegic patients (Picht et al. 2011b).

Lastly, the most important limitation of DTI FT is represented by the brain shift during surgery (Nimsky et al. 2005; Romano et al. 2011; Bozzao et al. 2010). This is unavoidable unless using intraoperative imaging and consists of an inward or outward displacement of the brain and therefore of the CST, especially in the final stages of surgery. Nevertheless, the intraoperative visualization of the CST must be considered exclusively as visual guidance for subcortical DES that still remains the gold standard for guiding lesion resection. However, the stronger correlation of nTMS-based DTI FT with subcortical DES makes it more accurate and therefore useful during surgery as compared to the standard DTI FT.

6.6 Conclusion

The functional nTMS-based DTI FT is more reliable and accurate for the reconstruction of the CST than standard anatomical tractography. The anatomical and functional details obtained through this somatotopic reconstruction enable a preoperative preliminary assessment of the spatial relationship between the lesion and parts of the motor fibers and improve the evaluation of the risks of tumor resection. Moreover, the nTMS-based DTI FT of the CST can be successfully used during surgery as a guide for orienting DES and lesion resection. In particular, the somatotopic organization of the CST may be used for improved neurophysiological exploration and to guide the EOR according to a preoperative plan. The influence of DTI FT on the extent of tumor resection remains an important issue to be addressed.

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Risk Stratification by nTMS via Corticospinal Excitability in Motor Cortex-Related Surgery

7

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7.1 Introduction

Brain tumor growth within or close to the motor system can compromise its functional integrity considerably. This can alter CSE as a sign of impaired subcortical connections between the motor cortex and the spinal cord (Picht et al. 2012). And such impairment can increase the risk of surgery-related neurological deficits. Various methods of functional noninvasive neurovisualization were described to assess the risks of surgery within motor eloquent cortex prior to surgery (please also see Chap. 2 for details).

The technique of fMRI measures the neurological activation indirectly using BOLD signal that reflects increased local metabolism. Yet, tumor infiltration also affects the brain metabolism and oxygenation levels. Brain areas infiltrated by tumor affect fMRI hemodynamic response and neurovascular coupling thereby cause both false positive and false negative BOLD activities (Wehner 2013; Wengenroth et al. 2011; Lehericy et al. 2000; Ojemann et al. 1998). It was reported that fMRI is able to assess the risk of surgery by detecting the eloquent motor cortex and its relationship to the tumor (Mahvash et al. 2014; Petrella et al. 2006; Tomczak et al. 2000). However, the fMRI assessment of one center is difficult to reproduce in other hospitals due to different MRI manufacturers, protocols, and related software packages. This causes highly variable analysis paradigms, algorithms, and, therefore, results (Dinov et al. 2014; Kekhia et al. 2011).

PET imaging is able to assess the neurosurgical risks for tumors that may have heterogeneous histologic characteristics by evaluating the various aspects of CNS tumor metabolism including cell proliferation rate, tissue hypoxia, glucose metabolism,

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expression of amino acid transporters, and biosynthesis of cell membranes (Bisdas et al. 2013). Such metabolic mapping using PET may show different patterns of progression for gliomas even suggesting malignant transformation of particular tumor areas (Smits and Baumert 2011). Simultaneous acquisition of PET and MRI data guides the location of biopsies in order to avoid sampling errors leading to undergrading of the tumor. The surgical sampling in these heterogeneous histological sites provides satisfactory diagnostic value for CNS tumor grading (Catana et al. 2008). However, besides these clinical benefits, PET has insufficient sensitivity and specificity in the identification of eloquent brain areas adjacent to intracerebral lesions (Hou et al. 2006; Krishnan et al. 2004; Lehericy et al. 2000; Rutten and Ramsey 2010).

MEG is a reliable noninvasive tool for preoperative mapping; its results correlate well with nTMS and direct cortical stimulation as a gold standard (Tarapore et al. 2012a, b; Vitikainen et al. 2009; Yingling et al. 1999). Localization of the hand motor cortex using MEG adaptive spatial filter (event-related desynchronization of brainwaves in the β frequency band) showed good correlation with the intraoperative hand motor DES sites (distance from the preoperative localizations is within 1.6 cm) (Nagarajan et al. 2008). An MEG-based functional risk profile defines the minimal distance between the lesion margin and the motor MEG sources. Surgical decision-making is based on the MEG mapping-derived functional risk profile in combination with MRI findings, anatomic characteristics of the tumor, and pathological findings (Hund et al. 1997). However, the availability of MEG is limited: high costs of the device preclude its wide distribution (Kekhia et al. 2011).

In contrast to these methods of brain mapping, nTMS not only reveals the topographical relationship between tumor and cortex, but it can also assess the functional status of the motor system by measuring CSE (Picht et al. 2012).

7.2 Corticospinal Excitability

CSE can also be measured intraoperatively by monitoring MEPs during cortical and subcortical DES, which is an invasive technique but currently the gold standard for localizing, monitoring, and preserving the eloquent motor cortex and pyramidal tract (Yingling et al. 1999).

Various physiological parameters such as arousal (Amassian et al. 1989), muscle activation before stimulation (Kiers et al. 1993; Darling et al. 2006), and spatial attention (Amassian et al. 1989; Mars et al. 2007) influence CSE. Individual physical parameters are also known to be related to CSE and include coil-to-cortex distance (CCD) (Julkunen et al. 2012), coil location (Kiers et al. 1993; Devanne et al. 1997), coil orientation (Laakso et al. 2014), and coil tilt related to the head location (Thielscher et al. 2011).

Navigated TMS provides the opportunity to visualize and maintain the position of the nTMS coil precisely to the targeted muscle's representation on cortex and

adjacent tumor. This allows increasing the accuracy of nTMS motor mapping followed by nTMS-based DTI FT and assessing CSE (Julkunen et al. 2009). The following neurophysiological MEP parameters characterize CSE as measured by nTMS:

7.2.1 Recruitment Curve

Recruitment curve (RC) or stimulus-response curve of MEPs represents the state of facilitation of the motor system and input-output function of the motor cortex (Devanne et al. 1997; Kimiskidis et al. 2005). The RC is a result of plotting the relationship between stimulus intensity over the MEP amplitude. Figure 7.1 demonstrates the example of RC at different stimulation intensities. Changes in Na^+ and Ca^{2+} channel properties and the GABAergic and monoaminergic systems, like antiepileptic drugs, can affect this parameter of motor system excitability (Boroojerdi et al. 2001).

7.2.2 Cortical Silent Period

The CSP is the silent period in the EMG after an MEP, which is produced by a single suprathreshold stimulus (120–150% of rMT) via TMS of the motor cortex during active tonic contraction of a target muscle (Cantello et al. 1992). The duration of the CSP reflects excitability in cortical inhibitory circuits. In normal human subjects, the duration of CSP varies between 98.3 ± 50.4 ms (mean ± SD) (McDonnell et al. 2006) and 173.9 ± 3.0 ms (Sale and Semmler 2005) depending on stimulation intensity (120–150% rMT), age (CSP is longer in young subjects), MEP areas, and

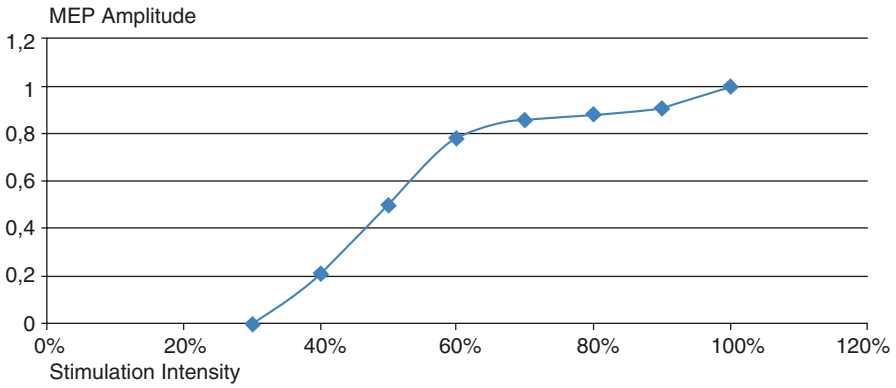


Fig. 7.1 Example of recruitment curve (RC). Plotting the relationship between the relative MEP amplitude and TMS stimulus intensity (30–100% maximum stimulator output)

current flow direction: anterior/posterior (Orth and Rothwell 2004). Resumption of EMG activity to its prestimulus level depends on the recovery of motor cortex excitability from GABAergic inhibition after TMS (Chen et al. 1999; Fuhr et al. 1991; Inghilleri et al. 1993; Orth and Rothwell 2004).

7.2.3 Resting Motor Threshold

The rMT is defined as the minimal magnetic pulse stimulation intensity, which is able to evoke an MEP of the target muscle as detected by EMG recordings in 50% of trials meaning five MEPs out of ten consecutive TMS stimuli. Usually, the MEP amplitude needs to be higher than 50 μV (peak-to-peak) (Awiszus 2003; Chen et al. 2008; Rossini et al. 1994). Differences of rMT between the left and right hemisphere reflect the ratio for excitability of neurons in the stimulated motor cortex areas and have clinical significance in the following pathologies:

- Stroke: Patients with mild to moderate hemiparesis 30 days after stroke have demonstrated an increase in rMT for a single magnetic stimulus over the ipsilesional M1 at the affected hemisphere in comparison to the unaffected hemisphere and compared to healthy controls (Cicinelli et al. 2003). These stroke patients have a strong inhibition of the affected hemisphere by the healthy one. Such imbalance in interhemispheric inhibition deteriorates motor deficits and affected the patients' potential for rehabilitation (Perez and Cohen 2009).
- Parkinson's disease (PD): Patients with PD and highly asymmetric muscle rigidity have significantly reduced rMT on the hemisphere contralateral to the more rigid side of the body, compared to the other side and to healthy control groups (Cantello et al. 2002).

Difference of rMT between the dominant and nondominant hemisphere is not statistically significant for healthy human subjects (Säisänen et al. 2008; Zdunczyk et al. 2013).

7.2.4 Interhemispheric rMT Ratio

The interhemispheric rMT ratio is the rMT ratio between the two hemispheres. It is calculated as the rMT (in % stimulator output) of the tumor hemisphere divided by the value of the unaffected hemisphere and expressed as a percentage. An rMT ratio of 90–110% is associated with equally excitable hemispheres and reflects the difference among young (age range: 19–31 years) and elderly (age range: 47–73 years) healthy individuals (Bashir et al. 2014) (Fig. 7.2).

For brain tumor patients, an rMT ratio of more than 110% and less than 90% reflects the imbalance of facilitation and inhibition of the M1 area or

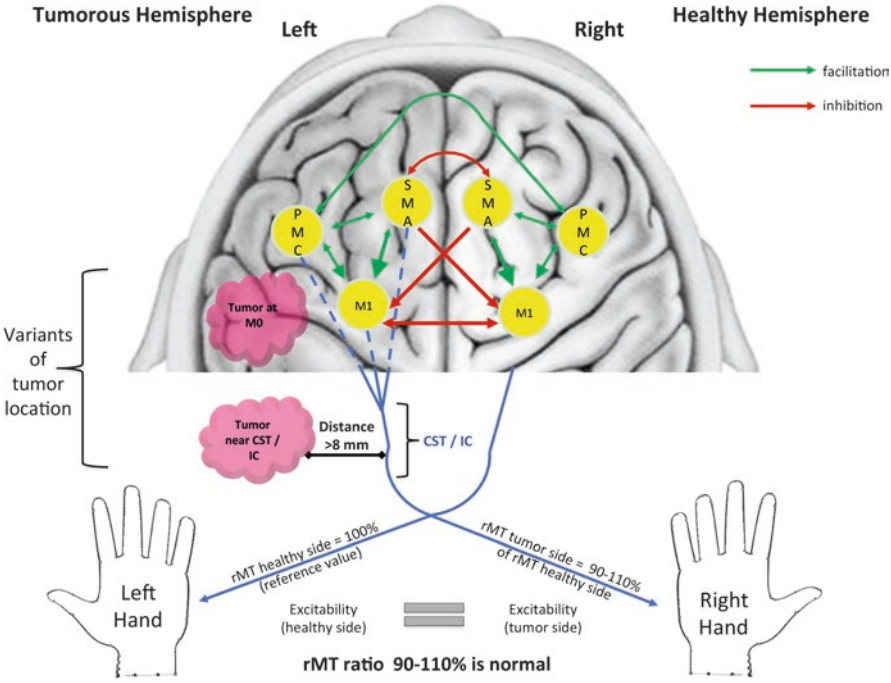


Fig. 7.2 Equally excitable hemispheres with normal interhemispheric rMT ratio 90–110%. The tumor does not affect the M1 (primary motor cortex) area, PMC (premotor cortex), or SMA (supplementary motor area) since the tumor is located at M0. Interhemispheric interactions for primary and secondary motor areas are in normal range. If located subcortically, the tumor has a distance to the CST (corticospinal tract) and IC (internal capsule) of >8 mm

secondary motor cortex (PMC plus SMA) of both hemispheres (Figs. 7.3 and 7.4). Figures 7.2, 7.3, and 7.4 schematically demonstrate variants of interhemispheric rMT ratios related to different brain tumor locations based on research of interhemispheric interactions in healthy volunteers (Grefkes et al. 2008) and modeling of its changes caused by tumor growth (Picht et al. 2012). All three figures show different mechanisms of how tumor growth in motor areas can affect CSE bihemispherically.

Figure 7.2 represents the "physiological CSE." PMC, SMA, and M1 areas are not functioning autonomously. They get facilitation (green arrows) and inhibition (red arrows) from each other and from homologous contralateral areas. The tumor does not affect the CSE because it is located outside of these areas (at M0) and has a safe distance to the CST (more than 8 mm).

Figure 7.3 demonstrates effects of an "M1 tumor." Tumor location affecting M1 causes an imbalance of facilitation and inhibition between both hemispheres that results in an increased CSE and decreased rMT on the tumor hemisphere.

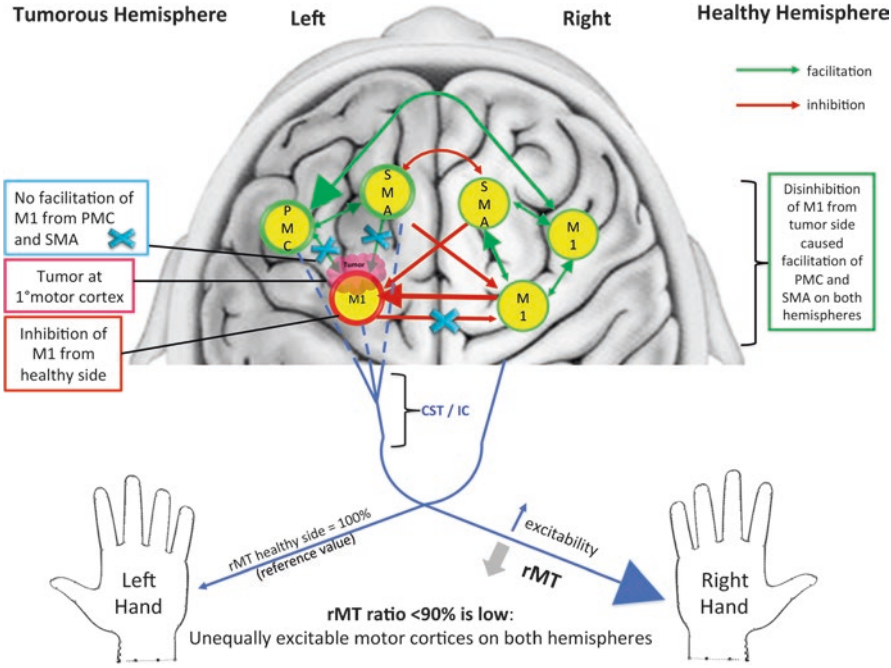


Fig. 7.3 Unequally excitable hemispheres with low interhemispheric rMT ratio <90%. The tumor affects the M1 area. Interhemispheric interactions of M1 and M2 demonstrate that the tumor impairs pathways of facilitation from M2 (PMC and SMA) to M1. Due to the facilitation of ipsilateral PMC, the affected hemisphere requires reduced levels of stimulation to produce movement, thus showing low rMT and low rMT ratio

This is reflected in the low nTMS-derived interhemispheric rMT ratio (less than 90%).

Figure 7.4 shows how tumors affecting the PMC and SMA proper or their descending pathways affect the CSE. While this tumor location facilitates SMA and M1 contralaterally to the tumor leading to an increased CSE on the healthy side, the ipsilateral M1 does not get facilitation from PMC and SMA due to tumor disruption. On the contrary, the ipsilateral M1 is inhibited by the contralateral M1, which causes decreasing CSE and in increased rMT on the tumor side, reflected by a high rMT ratio (more than 110%).

The nTMS technique provides the opportunity to assess these neurophysiological interdependencies in respect to the topographical relationship of eloquent motor cortex and tumor. Such neurophysiological "mapping" is able to supplement the risk assessment of the upcoming surgery and predict the likelihood of postoperative neurological outcomes by objective numerical parameters of the motor system's functional status. This model of risk stratification has been based on calculating the individual probability for a certain postoperative motor outcome 7 days and 3 months after surgery (Rosenstock et al. 2017).

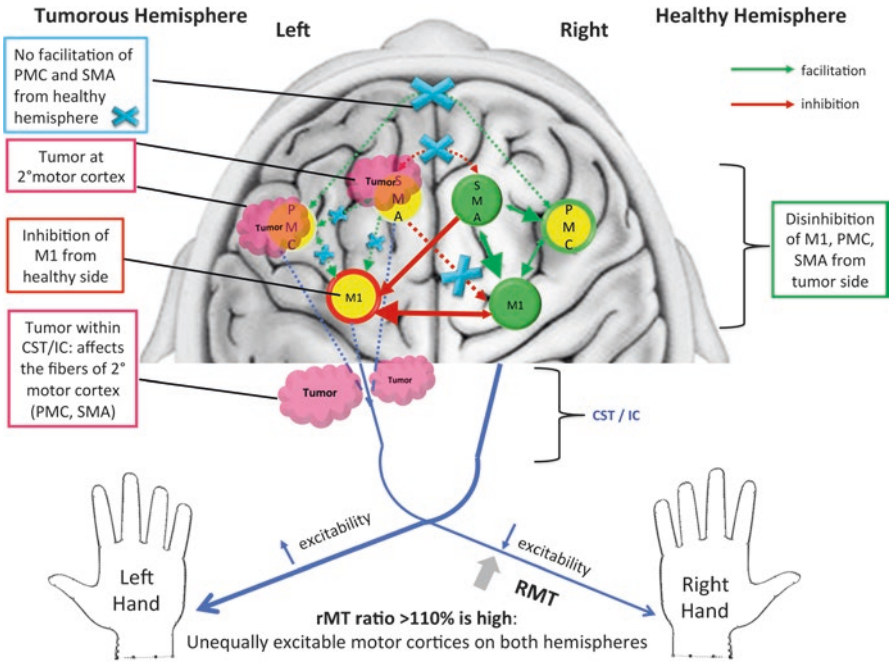


Fig. 7.4 Unequally excitable hemispheres with high interhemispheric rMT ratio >110%. The tumor affects M2 (PMC or SMA) due to its location. For subcortically located tumor, the distance to CST and IC is usually <8 mm. Interhemispheric interactions demonstrate the tumor-induced functional impairment: pathways of facilitation from M2 (PMC and SMA) to the ipsilateral M1 and inhibitory pathways from M2 (PMC and SMA) to the contralateral M1. The affected hemisphere requires increased levels of stimulation to produce movement, thus showing a high rMT and rMT ratio

7.3 Distance to CST and Risk Assessment

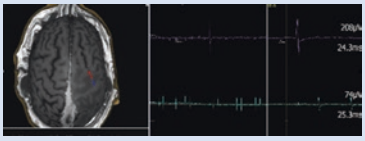
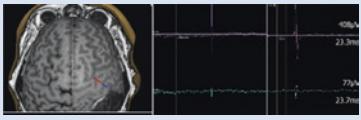
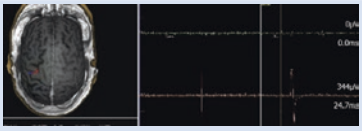
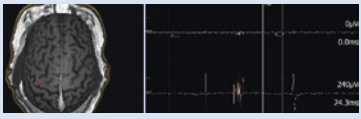
The distance between the tumor and the CST as visualized by nTMS-based DTI FT can also be used in terms of risk assessment. If this distance is 8 mm or more, resection is considered safe and any surgery-related paresis is highly unlikely (Table 7.1; Figs. 7.5 and 7.6) (Frey et al. 2014; Rosenstock et al. 2017).

7.4 Clinical Application

Obtained objective numerical data can be used for counseling patients, presurgically balancing risks and benefits and the planning of surgeries.

Patients without motor deficit before surgery, with similar tumor locations and comparable EOR during surgery, but with different rMT ratios on preoperative nTMS mapping can have different postoperative motor outcomes. Two clinical cases are provided as an example in Table 7.1.

Table 7.1 Illustrative cases

Variable	Patient #1 72 years old, female	Patient #2 41 years old, female
Diagnosis	Right temporoparietal glioblastoma WHO° IV	Right temporal glioblastoma WHO° IV
Preoperative motor status	BMRC grade 5—normal motor function	BMRC grade 5—normal motor function
nTMS-based DTI fiber tracking	Distance from tumor to CST >8 mm Please see Fig. 7.5	Distance from tumor to CST >8 mm Please see Fig. 7.6
rMT ratio = rMT tumor hemisphere/ healthy hemisphere	rMT ratio 78% <90% is low/ pathologic	rMT ratio 91% is normal (90–110%)
	rMT ratio = rMT tumor hemisphere (right) 21% stimulator output/rMT healthy hemisphere (left) 27% stimulator output = 78%	rMT ratio = rMT tumor hemisphere (right) 31% stimulator output/rMT healthy hemisphere (left) 34% stimulator output = 91%
	 rMT tumor hemisphere (right) 21% stimulator output	 rMT tumor hemisphere (right) 31% stimulator output
	 rMT healthy hemisphere (left) 27% stimulator output	 rMT healthy hemisphere (left) 34% stimulator output
Extent of resection	STR: 2 mm of residual contrast-enhancing tumor tissue on T1-weighted images	GTR: no residual contrast-enhancing tissue on T1-weighted images
Postoperative motor status after 7 days	BMRC grade 4 Worsening: left-sided hemiparesis	BMRC grade 5 No new motor deficit
Conclusion	Low rMT ratio can indicate that the tumor growth, its mass effect or edema can compromise the functional connectivity of the motor system. These deteriorations of CSE can be asymptomatic with normal motor status. However, the motor system's capacity for compensation can also be exceeded	Normal rMT ratio can indicate a compensated functional status: the integrity of the motor system is preserved in response to a growing brain tumor

Comparison of two clinical cases with similar tumor locations and preoperative motor status but with different rMT ratio and different motor outcomes. The rMT is given in % stimulator output. *BMRC* British Medical Research Council, *STR* subtotal resection

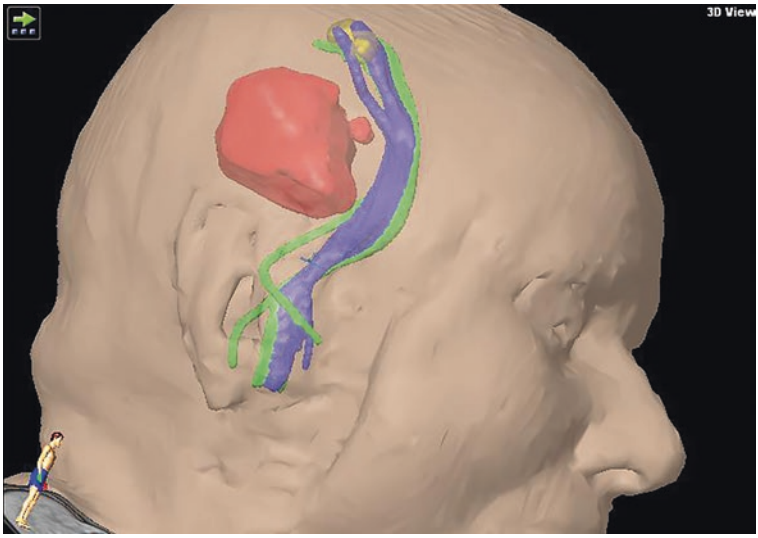


Fig. 7.5 Patient #1 of the illustrative case. Patient with a right temporoparietal glioblastoma WHO° IV and a distance from tumor to CST is <8 mm

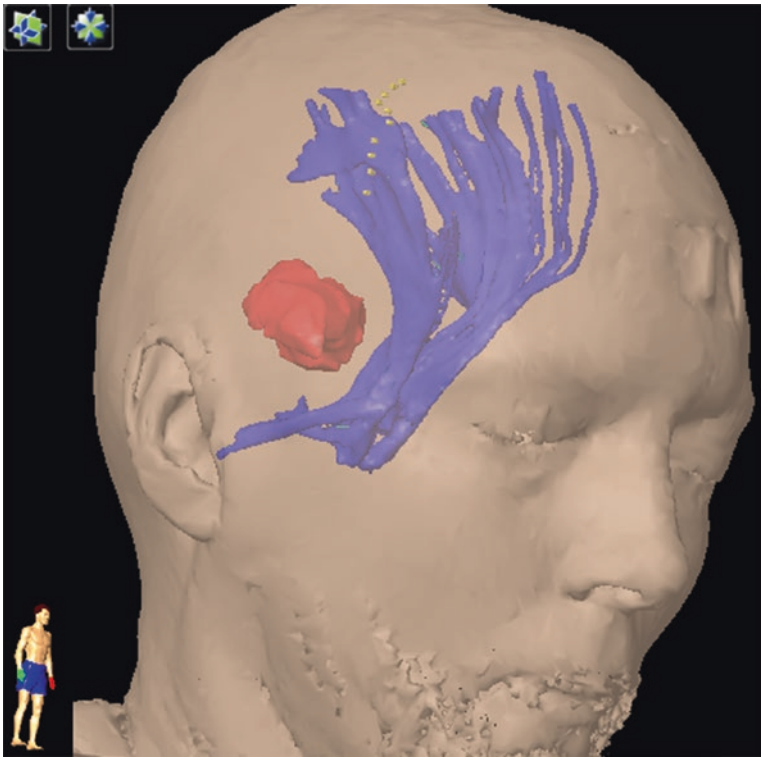


Fig. 7.6 Patient #2 of the illustrative case. Patient with a right temporal glioblastoma WHO° IV and a distance from tumor to CST is >8 mm

7.5 Conclusion

The determination of the interhemispheric rMT ratio can be easily implemented in the preoperative workup. The same nTMS device can measure the CSE, which is topographically correlated with the standard protocol of nTMS motor mapping.

The use of nTMS does not only provide the information about functional-anatomical relationships between brain tumors and adjacent eloquent areas; it can also assess the functional status of the motor system by measuring various parameters which characterize CSE like MEPs, RC, CSP, and rMT.

The interhemispheric rMT ratio as a component of risk stratification in motor cortex-related surgery can be used to calculate the individual probability for postoperative motor outcome.

Further research on other parameters of CSE using nTMS in neuro-oncology will allow to assess interactions between growing tumor and adjacent neural tissue more accurately. Such neurophysiological nTMS-based data will impact the indication for neurosurgical interventions, surgical planning, treatment modification, open up novel treatment options in case of surgery-related motor deficits and—as a consequence—on improve our patients' outcome, survival, and quality of life.

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Part III

nTMS Language Mapping

nTMS Language Mapping: Basic Principles and Clinical Use

8

Jyrki P. Mäkelä and Aki Laakso

8.1 Anatomy and Physiology of Language

Mapping of language-processing areas in the human brain has been going on since the early nineteenth century. The prevailing model of language processing in textbooks includes the frontal Broca's area and the temporoparietal, loosely defined Wernicke's area (Bogen and Bogen 1976) in the left hemisphere and their connections in the arcuate fascicle. The "Lichtheim house" model from the late nineteenth century (Lichtheim 1885) emphasized the importance of connections between the language-related areas and included, aside from these components, a less specified area for processing language concepts, encompassing large areas in both hemispheres (Graves 1997). These models were based on data obtained from the brain lesions' effects in patients, and the link between language disorders and focal brain lesions sometimes supports and sometimes refutes these constructions. The models have been criticized from the time of their emergence as simplified psychomorphological assumptions, and theories based on hierarchical development of psychic associative processes, such as language by Hughlings Jackson, Goldstein, and Luria, have emphasized less localized language presentations in the brain (Luria 1964).

The physiological basics of all language aspects are difficult or impossible to study in animal models. The development of modern brain imaging techniques, particularly fMRI and DTI, therefore provided a clear change in modeling the

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language representations in the brain. The present models include a frontoparietal "dorsal stream" involved in mapping sound onto articulation-based representations and a "ventral stream" in the temporal lobes, which maps sound onto meaning; particularly, the ventral stream seems to have a clear representation in both hemispheres (Hickok and Poppel 2007).

Language representations in the brain have also been studied in association with neurosurgery when operating tumors in the vicinity of the presumed language-eloquent areas. Under local anesthesia, the exposed cortex is stimulated directly via DES, and the effects of stimulation on the patient's language are tested. These studies (e.g., Ojemann et al. 1989) have revealed strong individual differences in the cortical sites producing language disturbances. They pinpoint small, clearly delineated mosaic-like areas in traditional language-related cortical areas and in the frontal lobe and middle parietal regions. Speech arrests can be observed in the ventral prefrontal cortex, not in the typical Broca's area; anomia/aphasia can be induced from the Wernicke's area, from the middle frontal gyrus (MFG) and inferior frontal gyrus (IFG), and from the superior temporal gyrus (STG). Moreover, right hemisphere stimulation in homologous areas induces language disturbances as well (Tate et al. 2014). This individuality has been considered to explain a variability of language disturbances and their recovery after relatively similar lesions and emphasizes that language areas cannot be localized only on an anatomical basis. These data have led to the recent paradigm shift from the traditional localizationist view of language function located in specific cortical regions toward a view of parallel, highly dynamic, cortico-cortical and cortico-subcortical networks supporting speech and language function (Duffay et al. 2014). The preservation of the main language tracts' functional integrity seems to be at least equally important to the preservation of cortical function. Nevertheless, even probing cortical and subcortical areas by DES is not always sufficient in preserving language integrity in neurosurgical procedures: new postoperative chronic language disorders have been reported in 11% of previously asymptomatic patients, despite DES during awake craniotomy (Ilmberger et al. 2008).

The knowledge of where language processing occurs in the brain does not clarify how language processing is done. This question has been investigated by various electrophysiological studies. The analysis of language-related evoked EEG and MEG responses has been used to estimate the timing of language-related activations in the brain. A sequential model of processing language within 200–600 ms has been comprised based on these studies (Indefrey 2011); this model is also supported by local intracranial field potential recordings (Sahin et al. 2009). Nevertheless, it is highly probable that parallel processing of various language-related phenomena occurs as well. The neural access to word representations in the left perisylvian language-related cortex can already occur 70 ms after language-related stimuli (Shtyrov and McGregor 2016).

Recent studies emphasize the role of the brain's oscillatory activity in language processing. In auditory processing of language-type stimuli, it appears that 4 Hz MEG oscillations present syllables, whereas words formed from these syllables are coded with 2 Hz activity and sentences with 1 Hz activity; similar oscillatory activities can be recorded from subdural grids with the same stimuli from broad cortical

areas including the temporal and frontal lobes in both hemispheres (Ding et al. 2016). Features of syllables may be determined by mechanical units of the language apparatus, defining natural oscillatory rhythms; natural mandibular cycles occur at about 4 Hz (Giraud et al. 2007). The oscillatory rhythms may also join language processing between different sensory modalities (Giraud and Poeppel 2012): when visual language input correctly predicts auditory language signals, a 3–4 Hz MEG activity develops over high-order language areas (Arnal et al. 2011). The importance of oscillatory brain activity in processing language is further emphasized by observations suggesting that spectral ECoG mapping from subdural grid electrodes may identify crucial language-related areas better than the stimulation of the grid electrodes (Cervenka et al. 2013).

Studies using rTMS to analyze language processing have found 4–8 Hz stimulus trains to be the most effective in disturbing language (Epstein et al. 1996; Devlin and Watkins 2007). In our preliminary tests, nrTMS in this frequency range is effective and well tolerated in the search of language representations in healthy subjects and patients.

8.2 nrTMS Language Mapping in Healthy Subjects

The nTMS technique induces currents within the cortex in an area identified from the subject's or patient's own 3D brain MRI reconstruction (Ruohonen and Karhu 2010). The physiological changes induced by TMS and rTMS are qualitatively similar to those induced by DES. Consequently, preoperative noninvasive nTMS and nrTMS could be potentially well matched with DES, the current gold standard for neurosurgical functional localization. The clinical experience from DES suggests that object naming is the most useful and sensitive experimental setup to map the language-related cortical areas intraoperatively (e.g., Petrovich Brennan et al. 2007). We have developed a protocol for preoperative localization of language-related cortical areas by utilizing object naming and nrTMS combined with video recording of the behavioral results (Lioumis et al., 2012). A commercial setup (NexSpeech™, Nexstim Plc., Helsinki, Finland) is in use in more than 40 neurosurgical centers around the world.

8.2.1 Methodology and Execution

Color picture sets, normalized over visual and linguistic parameters (e.g., Brodeur et al. 2010), are displayed to the subject on a computer screen. The subject or patient has to name these pictures as quickly and precisely as possible. The experiment starts with baseline sessions without nrTMS, followed by active nrTMS sessions. Both are video recorded for later offline analysis. Unfamiliar or incorrectly named images in the baseline session are removed from the image set, and only fluently named images are used during nrTMS. The stimulation is done with 1–2 s nrTMS pulse trains of 5–10 Hz delivered simultaneously or after the picture onset. The stimulus intensity

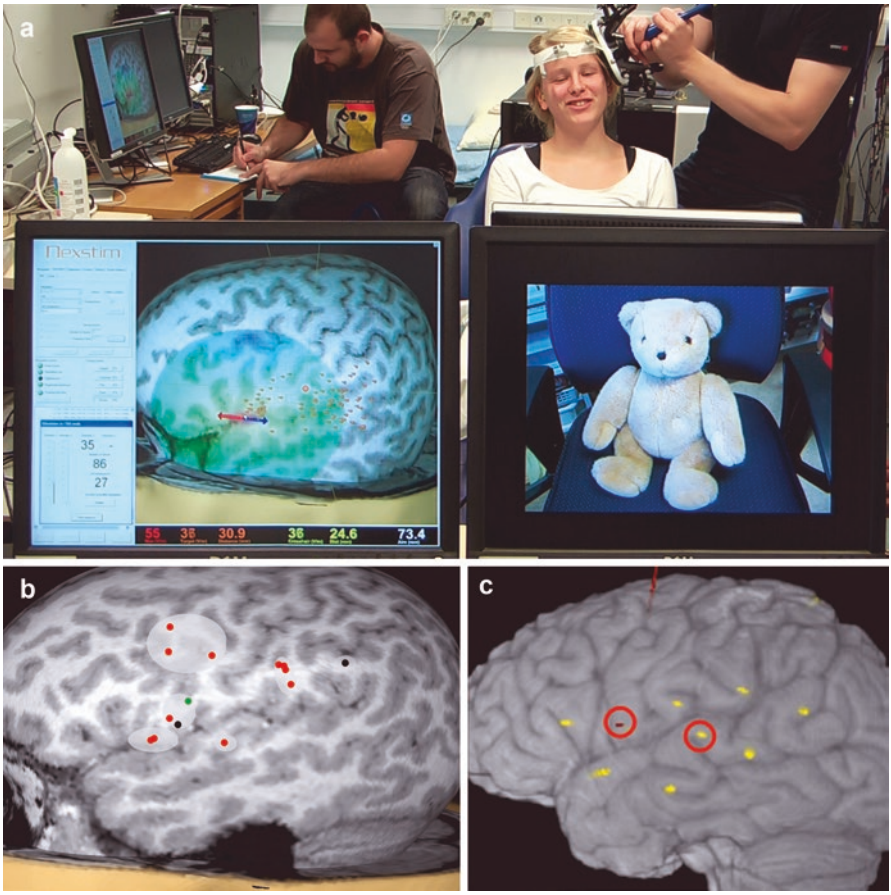

Fig. 8.1 Setup of nrTMS language mapping. (**a**) depicts the prototype of the setup for videoed nrTMS mapping of language-related cortex in BioMag Laboratory. The nrTMS to the participant's left frontotemporal region blocks naming of the presented object (modified from Lioumis et al. (2012)). (**b**) The nrTMS sites that disturb naming displayed on a 3D MRI of a patient with intractable epilepsy. *Red tags*: sites producing anomia. (**c**) Stimulation of depth electrodes surrounded by *red circles* elicited anomia in the patient (courtesy of Liisa Metsähonkala)

over different brain regions is calibrated by the strength of the electric field induced within the cortex. The coil is handheld and moved freely between the pulse trains. Usually, about 200–300 sites are stimulated within one hemisphere by moving the coil semirandomly between the pulse trains, following a grid-like pattern so the tested target sites systematically cover a wide cortical area (Fig. 8.1; for videos of the experiment, see Lioumis et al. 2012; Hernandez-Pavon et al. 2014), not limited to traditional areas defined by the Geschwind language model. The baseline naming responses are compared with those recorded during nrTMS. The types of nrTMS-induced errors are classified; the corresponding nrTMS locations in the parcellated cortex are marked as language-related and are tagged by the observed error type (for details, see Corina et al. 2010; Picht et al. 2013).

Several things need to be taken into account to obtain useful results.

1. The pictures that are not named adequately in the baseline session need to be removed from the image stack for the following mapping.
2. The interpicture interval (IPI) needs to be adjusted so that the task is not too easy (start with 2.5 s, vary between 1.5–4 s).
3. Match the depth and induced electric field intensity (in V/m) of the target area to the same electric field intensity of the rMT for hand muscles at the cortical hand motor hotspot; stronger stimulation is often required for parietal than for fronto-temporal targets to reach corresponding electric field intensities.
4. Keep the induced electric field in anteroposterior direction, and monitor the coil tilt so that the coil center is not in the air.
5. Keep the coil in the same spot for 2-3 nrTMS trains if some performance differences are induced.
6. Change the coil orientation if the effect of the stimulation implies an active area (e.g., slight hesitation or louder voice during naming due to an increased effort), but no clear errors are detected.
7. Do not stimulate the same site for a long time. Move away and return to test the site again.
8. Stimulate regions further from the lesion and anatomically presumed language areas to identify possible language sites that have spatially shifted due to plastic changes induced by the lesion if the patient has a large tumor (or other lesion).

Sometimes the initially selected parameters do not produce language perturbations and require adjustments. It is prudent to start with increasing task difficulty by reducing the IPI, continue with an increase in nrTMS train frequency (from 5 to 7 to 10 Hz), reduce stimulation onset time (=picture-to-trigger interval; PTI) from 300 to 200 to 100 ms after the picture presentation for fast-naming patients, and finally increase in nrTMS intensity if the patient tolerates it. It is also useful to have more ambiguous picture sets available to increase the cognitive demands of the task if needed.

8.2.2 Results

The nrTMS mapping finds language-sensitive cortical sites most often in the IFG, STG, and supramarginal gyrus (SMG). There is a clear individual variability in the sites where nrTMS induces language disturbance, paralleling individuality seen in DES results during awake surgery (Sanai et al. 2008; Corina et al. 2010). The methodology also provides an accurate monitoring and high-fidelity report of behavioral nrTMS experiments. It enables an unbiased offline analysis of stimulation effects, as the stimulation sites can be blinded during data analysis. It is easier to recognize semantic and phonological paraphasia and performance errors from the video than during the measurement. Occasionally, the subjects smile or move their lips or jaw during anomia, indicating that no motor speech arrest is induced by nrTMS. Poststimulus consultation of the subject about the nrTMS-induced experiences and sensations is also feasible with joint viewing of the video recording. This

is particularly useful in separating the pain-induced changes (see below) from the true effects of nrTMS. The language nrTMS spatial resolution, evaluated from experiments in healthy subjects, suggests that language nrTMS is precise enough to evaluate language-related cortical areas on the gyral level (Sollmann et al. 2016a).

The naming performance in some healthy subjects is quite resistant to nrTMS. Object naming is more sensitive to nrTMS-induced disturbances than action naming (Hernandez-Pavon et al. 2014; Hauck et al. 2015a). Some anecdotal observations indicate that the secondarily rather than the primarily learned language is more easily disrupted by nrTMS. The sites interfering with naming also occur in the right hemisphere; the functional significance of these nondominant hemisphere sites is unclear (Rösler et al. 2014; Sollmann et al. 2014). The methodology, therefore, provides ample opportunities for basic research. As the active sites vary considerably between subjects, adequate intra- and interindividual statistics are useful for their analysis (cf. Hernandez-Pavon et al. 2014).

Types of naming errors may vary between repetitions of the stimulation of the same site (Fig. 8.2). Moreover, personal reports about the language difficulties

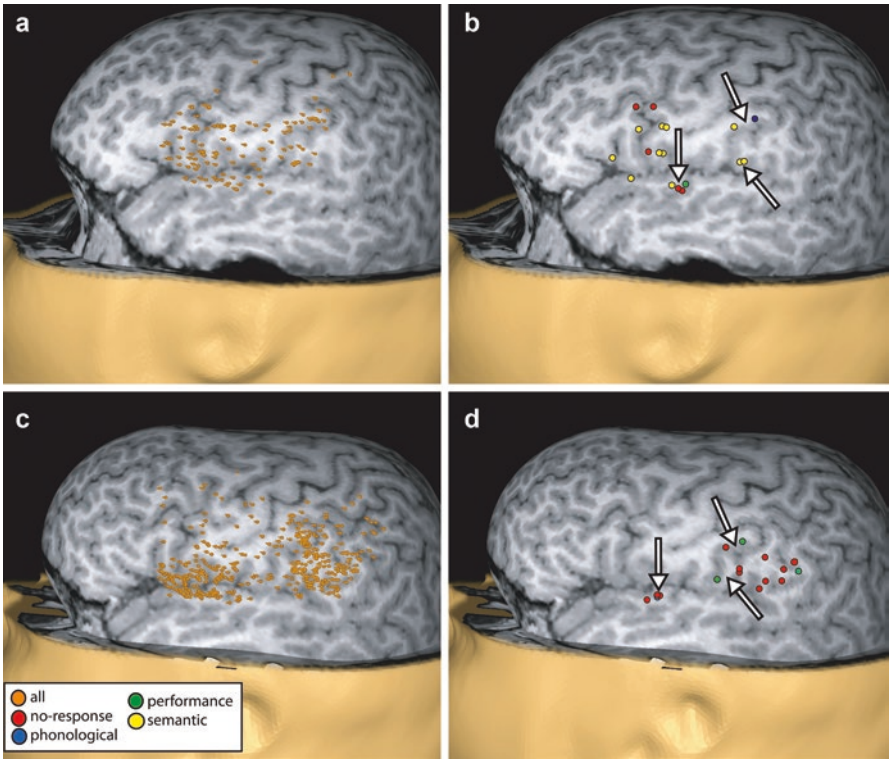

Fig. 8.2 Reproducibility of nrTMS language mapping in a healthy subject. (**a**) and (**c**) illustrate all stimulated sites in two sessions, and (**b**) and (**d**) illustrate the sites producing language disturbances in them. The *arrows* point to areas sensitive to nrTMS. Different error types are *color-coded*; *all* indicates all stimulated sites. Note that within the sensitive areas, the error types vary between the two measurements (modified from Lioumis et al. (2012))

induced by nrTMS to language-sensitive sites include reports of not remembering the word—in the same manner as meeting a familiar face but not connecting it to the person's name. Attention modulations during naming may produce errors similar to that induced by nrTMS. As attention enhances blood flow changes in language-related areas during word processing (Alho et al. 2003), decrease of attention may produce similar effects as nrTMS. Additionally, nrTMS targeted to the dorsal attention network is known to disturb semantic decisions (Capotosto et al. 2016). These features indicate that nrTMS may affect language on several processing levels.

8.3 nrTMS Mapping in Patients

Language mapping by nrTMS, combined with video recordings, has been applied in preoperative functional localization in patients with tumors close to the perisylvian language-related cortex. This approach has been compared to DES during awake craniotomy (Picht et al. 2013; Tarapore et al. 2013), and the results appear promising, though not as systematic as those obtained in nTMS mapping of the motor cortex. The method is well tolerated in most adult subjects. The youngest patient with successful preoperative language mapping in BioMag Laboratory was 6 years old.

8.3.1 Special Issues Related to Patients

The main indications for preoperative nrTMS language mapping are tumors located in "classical" language areas, that is, the left perisylvian cortex, especially in the frontal operculum and temporoparietal region (Hervey-Jumper et al. 2015). Nevertheless, evidence regarding relevant speech and language function outside of these areas, also in the nondominant hemisphere, is increasing (De Witt Hamer et al. 2012; Desmurget et al. 2007; Southwell et al. 2016; Cogan et al. 2014).

Maps and individual nrTMS-positive sites for language can be imported into the neuronavigation and hospital PACS via DICOM standard for data storage and flexible use by different hospital departments (Mäkelä et al. 2015). The nrTMS-positive spots can, for example, be transferred into the neuronavigation system of the neurosurgical operation room to add functionality to the anatomical visualization or to be used as seeds for mapping the white matter tracts via DTI FT to be avoided during surgery (Fig. 8.3, Frey et al. 2012) (please also see Chap. 9). The nrTMS experiment prepares the patient for the forthcoming awake craniotomy, as the procedures of stimulus presentation, stimulation, and experience of language impairment are highly comparable.

Moreover, the nrTMS data enables consulting the patient preoperatively about the possible risks of extensive operation versus remaining tumor tissue. Some patients feel empowered by the possibility to make such decisions about their treatment on the basis of detailed visualization of their functional anatomy.

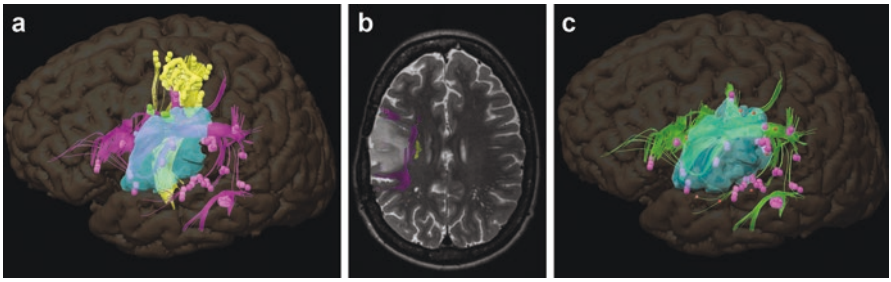

Fig. 8.3 Illustrative case. Data from a 48-year-old female patient with a recurrent oligoastrocytoma in the dominant left frontal operculum. Before awake surgery, she underwent nr/nTMS for language and motor mapping. (**a**) The tumor outline is in *cyan*, language-positive nrTMS points are in *purple*, face motor nTMS points are in *green*, and hand motor nTMS points are in *yellow*. Tractography was performed using nr/nTMS points as seed ROIs: the arcuate fascicle portion of the superior longitudinal fascicle is in *purple* (generated with nrTMS language data), and the CST is in *yellow* (generated with nTMS motor data; additional ROI in the left side of the pons). (**b**) A T2-weighted axial MRI of the same patient, demonstrating nrTMS language points and the arcuate fascicle in *purple* and CST in *yellow*. (**c**) The same patient with language-positive nrTMS points in *purple* and arcuate fascicle in *green*. *Smaller red points* indicate the navigated intraoperative sites where DES elicited repeatable naming errors (anomia and paraphasia) using 3 mA and 50 Hz monopolar stimulation. Note that 1.5 T MRI images were processed using Brainlab iPlan Cranial 3.0 software (Brainlab, Munich, Germany)

8.3.2 Validation

The mapping of language-related cortical areas by nrTMS has been compared to DES during awake craniotomy in patients with brain tumors (Picht et al. 2013; Tarapore et al. 2013; Ille et al. 2015). The use of nrTMS language mapping is sensitive but relatively nonspecific in detecting the sites producing language disturbance in DES. The first published comparison of the two methods in 20 patients found a sensitivity of 90%, specificity of 24%, positive predictive value (PPV) of 36%, and negative predictive value (NPV) of 84% of nrTMS to predict intraoperative DES mapping results during awake surgery (Picht et al. 2013) using the cortical parcellation system (CPS) (Corina et al. 2010). False-negative findings in comparison with DES were sparse and focused mainly on high parietal areas (Picht et al. 2013). Another study of 12 brain tumor patients also compared nrTMS object naming with intraoperative DES mapping results during awake surgery. In these patients, nrTMS was tested at 465 sites; 21 induced language errors. In two patients, no positive sites were found. DES was tested in 221 sites and ten of them were positive. No positive sites were found in three patients. Nine DES sites corresponded to positive nrTMS sites, one did not; four nrTMS-positive sites corresponded to negative DES sites; 169 sites were negative both in nrTMS and DES. Thus, nrTMS specificity was found to be 90%, sensitivity 98%, PPV 69%, and NPV 99% (Tarapore et al. 2013). These excellent results, particularly in specificity, may be due to starting the nrTMS simultaneously with the picture onset (see also Krieg et al. 2014a) and limiting the distance between the compared DES and nrTMS sites to 1 cm instead of using the

cortical parcellation system. Ille et al. (2015) found a sensitivity of 97%, specificity of 15%, PPV of 34%, and NPV of 91% for nrTMS with comparison to DES in 27 brain tumor patients (Ille et al. 2015). In six patients with epilepsy, nrTMS predicted DES results with a sensitivity of 67%, specificity of 66% PPV of 24%, and NPV of 95% (Babajani-Feremi et al. 2016). Our experience regarding 20 patients with epilepsy surgery planning suggests similar values (Henri Lehtinen, pers. comm.).

Throughout these studies, a high NPV has been a consistent finding, indicating that nrTMS produces reliable "negative maps" sufficient to plan brain tumor and epilepsy surgery.

8.3.3 Clinical Use of nrTMS Data

Cortical sites where repeated nrTMS could not disrupt language processing in an object-naming task appear to correspond rarely to language-eloquent sites in intraoperative DES, suggesting a high correlation of "nrTMS language-negative" brain regions with intraoperative DES (Krieg et al. 2014a; Picht et al. 2013). Clusters of induced language disturbances occurring within the same cortical area indicate that the area is probably relevant for language processing. Isolated single deviations from the baseline performance indicate a need for further examination of the area by DES. Moreover, nrTMS language mapping may be helpful for surgical planning via nrTMS-based DTI FT for subcortical language tracts (Fig. 8.3; see also Chap. 9) (Negwer et al. 2017; Frey et al. 2012; Raffa et al. 2016).

It is prudent to export nrTMS-positive stimulation points to the neuronavigation system at cortical and subcortical depth of the 3D MRI to better visualize their location in various angles. A standard color-coding of the nrTMS language mapping data eases functional anatomy interpretation.

The preoperative nrTMS mappings of language-related cortical areas are in routine clinical use in our hospital. The nrTMS maps are incorporated into neuronavigation planning software and are used as ROIs for tractography (Fig. 8.3). During surgery, cortical mapping with DES starts at nrTMS-positive spots integrated into the neuronavigation (please also see Chap. 3). This usually facilitates rapid identification of positive DES sites and the required threshold current to elicit motor and language responses by DES. In cases in which eloquent areas are shifted from their presumed classical anatomical regions due to tumor- or epilepsy-induced plasticity, it is very comforting for the neurosurgeon to have this information preoperatively, as it eliminates confusion and uncertainty during surgery. It is also worth noting that because the nrTMS effect depth is several millimeters, it may sometimes be unclear which of the adjacent gyri on opposite sides of a sulcus is actually responsible for the observed nrTMS response. Naturally, the fusion of nrTMS data with the intraoperative neuronavigation system has limitations due to brain shift, particularly during tissue resection.

Although the surgeon does not rely on tractography during resection, the provided information regarding location and direction of functionally crucial fiber tracts greatly facilitates intraoperative subcortical DES, which starts at the sites

superficial to the tracts, using stimulation currents sufficient to elicit responses at safe distances. A current of 1 mA stimulates white matter tracts at the depth of approximately 1 mm (Kamada et al. 2009). We usually start locating the subcortical tracts with a current of 10–15 mA and estimate the distance to the tract on the basis of the current strength required to elicit responses. The resection is halted latest when the threshold current reaches 2–3 mA and, preferably earlier, at approximately 5 mA, to avoid permanent tract injury.

The nrTMS efficacy to map the language-related cortical areas varies considerably between individuals and experimental setups (Sollmann et al. 2013b). The reported specificity values (Picht et al. 2013; Tarapore et al. 2013; Ille et al. 2015) vary between 15% and 98% and suggest strong effects of slight variations in paradigms and interpretations of the results between the different laboratories using the methodology. As the stimulation frequencies used in nrTMS language mapping are different from DES and the distance from the cortex is clearly longer, it is evident that a single nrTMS train does not give conclusive results about language sensitivity of any particular cortical site. Successful nrTMS language mapping is based on several nrTMS trains and meticulous observation and documentation of induced language changes, best done by video-based offline analysis (Lioumis et al. 2012). Final surgical decisions regarding the functional relevance of cortical tissue and subcortical fiber tracts are made based on the intraoperative mapping and monitoring results (Bello et al. 2007, 2014; Soffietti et al. 2010; Seidel et al. 2013).

Functional plasticity may be associated with the growth of brain tumors. This plasticity may permit a multistage resection of tumors several years after the first surgery (Robles et al. 2008). In nrTMS studies, it appears that patients with left hemisphere tumors appear to have more right hemisphere sites interfering with language during nrTMS mapping than healthy control subjects (Rösler et al. 2014; Krieg et al. 2013). The possible functional significance of these changes is unclear at present. First report on follow-up investigations by nrTMS showed plastic reshaping of cortical language areas after surgery (Kawashima et al. 2013). It has been suggested that surgical resection of brain gliomas may benefit from better understanding of the dynamic interaction between the tumor and the reactional plasticity of the nervous system as a result of both tumor invasion and surgery (Duffay 2005). Language mapping by nrTMS may provide a tool to gather such understanding.

Additionally, nrTMS induces more errors in patients with language disturbances than in those with fluent language (Rösler et al. 2014). It also appears that if the error rates induced by nrTMS are clearly higher in the left than the right hemisphere, surgery of the left hemisphere tumor harbors an increased risk of postoperative language disturbance (Ille et al. 2016). Thus, nrTMS may be useful in defining hemispheric lateralization of language processes in patients. It is worth noticing, however, that language-sensitive sites are found in the right hemisphere of most investigated patients (Rösler et al. 2014; Ille et al. 2016) even in those with left-dominant language representations found by other methods, including Wada test as the gold standard. The nrTMS mapping lateralization properties have not been systematically studied. Previous experience on nonnavigated TMS in lateralizing

language has been less than optimal (Epstein et al. 2000; for discussion, see Devlin and Watkins 2007).

So far, nrTMS language mapping has mainly been used for preoperative planning of tumor surgery. Yet, the sensitivity and specificity values of nrTMS language mapping to predict DES results in epilepsy surgery workup (Babajani-Feremi et al. 2016); H. Lehtinen, pers. comm.) are in line with those obtained in tumor surgery and suggest similar usefulness of nrTMS language mapping in planning epilepsy surgery.

The first report describing the use of nrTMS language mapping without awake craniotomy and DES has been recently published. No harmful postoperative deficits occurred in this small cohort of four patients (Ille et al. 2017).

The clinical usefulness of preoperative nrTMS language mapping is suggested by a study of two groups of 25 patients. Patients with an available nrTMS language mapping data had significantly smaller craniotomies and had less postoperative aphasia in the first postoperative days than those without nrTMS maps. No difference in outcome, however, was observed in long-term follow-up of the two groups (Sollmann et al. 2015b).

8.3.4 Comparison with fMRI and MEG

Chapter 2 extensively outlines these aspects. Thus, this section only focuses on the differences concerning language mapping.

Other preoperative noninvasive methods for functional cortical mapping, such as fMRI or MEG, rely on different physiological changes than nrTMS and DES. The combination of fMRI, MEG, and nrTMS may give a more complete picture of the pathophysiology and disease-related functional plasticity in patients with epilepsy (Mäkelä et al. 2013).

Language-related activations found by fMRI appear not to have a useful predictive value in estimating the results of DES in awake craniotomy (Giussani et al. 2010). Furthermore, nrTMS language mapping might be superior to fMRI in the vicinity of brain lesions (Sollmann et al. 2013a), as it is far less prone to artifacts based on increased vascularity and altered tissue oxygenation (Giussani et al. 2010; Picht et al. 2013; Ille et al. 2015). This may be particularly true for highly vascularized and high blood flow lesions, such as arteriovenous malformations (AVMs), which may extend to eloquent regions (Juenger et al. 2009; Kronenburg et al. 2014). This may also indicate that the language networks in the brain depicted by fMRI may contain both critical and participating areas (Mesulam 2000). These suggestions were supported by Ille et al. (2015), who described clearly lower sensitivity (40%) and NPV (79%) of language fMRI than nrTMS in the same patients (see above) in predicting the DES localization of the cortical language sites during awake surgery.

Tarapore et al. (2013) compared localization results of nrTMS with those obtained by MEG beta band suppression during picture naming and verb generation and with DES during awake craniotomy. MEG found 18 verb generation sites and 14 picture-naming sites. Seven MEG language sites correlated with nrTMS sites in

five patients and with DES in two patients; the result was clearly inferior compared with that of nrTMS and DES sites (see above).

8.3.5 Mechanism of the rTMS Effect

As outlined in Chap. 1, several mechanisms on how rTMS mediates its effects on the brain have been put forward. Concerning language mapping, the most favored suggests that rTMS induces a "virtual lesion" in the brain: no general agreement about exact mechanisms underlying the "lesion" is available, however. rTMS may induce an aberrant inhibition/excitation state of the stimulated cortical target (Harris et al. 2008), interfere processing by introducing random activity that competes with the neural activity coding the signal (Walsh and Cowey 2000), or activate the neurons that have not been activated by target stimulus, thereby reducing the signal-to-noise ratio and worsening stimulation detection (Silvanto and Muggleton 2008). It is also worth noticing that rTMS effects (and those of DES; see Borchers et al. 2012) are not restricted to target regions but spread to adjacent and anatomically connected regions (Robertson et al. 2003; Walsh and Cowey 1998; Ilmoniemi et al. 1997; Valero-Cabre et al. 2005). It is also perfectly feasible that rTMS modulates the ongoing oscillatory electric brain activity and interferes with normal brain processing. Rhythmic rTMS causes the local entrainment of natural EEG oscillations (e.g., Thut et al. 2011; Veniero et al. 2015). Brief 20 Hz rTMS trains may interfere with the suppression of alpha band oscillations associated with attention (Capotosto et al. 2016). If this is so, the effects of rTMS depend on the brain network state and may vary with its variance despite precisely the same stimulation parameters and site. This phenomenon may explain part of the nrTMS variability of effects at the same stimulation site (Fig. 8.2). Thus, rTMS–EEG in studies of language-related oscillatory activity may reveal clues of its physiological effects. It is not, however, clear what frequency ranges should be examined to this end. The most obvious choice is the theta frequency range induced by 4–8 Hz rTMS. Also, 10 Hz inhibitory alpha bursts, known to be associated with the interference of memory tasks by rTMS (Capotosto et al. 2016), may be worth studying.

8.4 Open Questions

Language mapping protocols for nrTMS vary somewhat between centers performing the examinations. This is related to varying results and hampers comparison of the results across centers and interferes with accepting the method in clinical use. An international workshop group of experienced clinical nrTMS users is preparing a recommendation of a joint protocol for further clinical studies (Krieg et al., In press).

In our experience, stimulation parameters may need to be adjusted according to individual properties of the tested subjects or patients; the best sensitivity may be obtained with slightly different stimulation frequencies in different patients. Some

patients name the images quite rapidly, and adjustment of the nrTMS pulse train timing may be needed. Some patients with preexisting language difficulties may need long intervals between the picture presentation and nrTMS train to be able to perform the task. These factors can usually be evaluated and tested during the baseline naming session. A quiet environment is useful to enable the full concentration on the naming task by the patient; it is difficult to separate nrTMS-induced naming changes from those due to fluctuating attention to the task. Fatigue and boredom due to several repetitions of the task may also influence the task performance.

We have induced language errors of some type in most patients with the nrTMS frequency parameters described above. Trains of nrTMS with higher frequency may also induce language disturbances (Rogic et al. 2014). Face muscle pain and tetanization may prevent high stimulation frequencies, particularly when long nrTMS trains are delivered (Devlin and Watkins 2007).

The level of discomfort or pain experienced during mapping is a crucial factor in interpreting the language mapping results; rTMS-induced pain may limit the spatial extent of nrTMS language mapping, particularly when stimulating the orbital and polar IFG (Krieg et al. 2016). A median visual analogue scale (VAS) score of 4.5 (0–10; 10 = maximum pain intensity) for the maximum experienced pain has been reported, but the discomfort of nrTMS was not considered distressing by most patients (Tarapore et al. 2016). Search for optimal stimulus orientation (usually perpendicular to the temporal muscle fibers to minimize contraction) or reduction of stimulation intensity usually enables mapping completion.

Small changes in stimulation site, orientation of the coil, and its tilt with respect to the head surface modify the strength of nTMS-induced MEPs (Schmidt et al. 2015). Similar sensitivity affects the nrTMS effects on object naming (Sollmann et al. 2015b). Also, stimulation frequency may influence the type of induced language disturbances (Hauck et al. 2015b). It is worth noting, however, that effects of sequential DES of the same site may vary considerably (Whitaker and Ojemann 1977; Lesser et al. 2008).

One source of nrTMS language mapping result variability may relate to the induced cortical electric field modeling, which identifies the cortical target area. This is done by localized spheres (Chap. 1). This type of modeling is fast to compute and is valid in brain areas with local sphericity, such as sensorimotor or parietal areas. It may, however, induce localization errors, for example, in nonspherical frontotemporal areas (Nummenmaa et al. 2013). As a result, source modeling error increases, and small changes in orientation may divert the actual created voltage to unexpected sites. Moreover, due to the physical properties of the induced fields, nrTMS is not able to directly stimulate deep frontal or temporomesial structures.

The parameters of the nrTMS language mapping protocols are still not fully optimized for clinical use. For example, the false-negative findings of nrTMS language mapping compared to DES are reported in mainly parietal regions. Use of action naming instead of object naming appears not to diminish this problem (Hernandez-Pavon et al. 2014; Hauck et al. 2015a), contrary to suggestions based on DES (Lubrano et al. 2014). The influence of delays between the presentation of the images to be named and the onset of the nrTMS pulse train (=PTI) is debated.

First, tests of inducing language perturbations with nrTMS were done with a 300 ms delay between the picture onset of an nrTMS to minimize the number of required nrTMS pulses and maximize the overlap of nrTMS and language processing, as the used coils had no cooling system and the coil heating limited the total number of deliverable pulses. Single-pulse nTMS to Broca's area delays naming significantly when delivered 225–300 ms after the picture onset, not before or after this time range (Wheat et al. 2013). In healthy subjects, varying the delay between images and nrTMS affects the type and distribution of the induced language disturbances (Sollmann et al. 2016b). DES typically aims for a 0 ms delay between image presentation and stimulation, though the stimulation is delivered manually, without automatized, precise time locking. The nrTMS experiments using a 0 ms PTI are producing language errors effectively and may increase sensitivity in the parietal areas compared with DES (Krieg et al. 2014a, b; Ille et al. 2015). This is not surprising, as the comparability between DES and nrTMS should be increased by increasing the similarity between the experimental setups. Yet, nrTMS may induce blinks, which may interfere with early image processing in the 0 ms paradigm (Corthout et al. 2003) and decrease specificity of the findings.

One problem of scoring the rTMS-induced changes in object naming is the evaluation of delayed responses. Inducing a 50 ms naming delay by rTMS of Broca's area is considered significant in basic research studies (e.g., Schuhmann et al. 2012), but such short delays are difficult to detect in visual analysis of language responses. Recently, an automated analysis of language-induced laryngeal vibrations by an accelerometer has been suggested as useful for this purpose (Vitikainen et al. 2015). It is not sensitive to nrTMS-associated coil clicks or environmental sounds, such as from the cooling system, and is thus preferable to recording vocalizations by a microphone. This method, however, has not yet been tested against DES recordings.

Brain tumors may be related to abnormal electric brain activity, and rTMS trains may induce such abnormal electric phenomena, though overt seizures are not observed. The same possibility is naturally present in patients with frequent epileptic seizures. Such changes might induce language disturbances, although the stimulated sites were not related to language processing. Systematic studies with rTMS–EEG might be useful in probing these alternatives. Up to now, no seizures were reported on nrTMS language mapping in a large, international cohort of patients (Tarapore et al. 2016).

A better understanding of the effects of nrTMS on language networks is probably required to clarify the open questions and benefits of its precise clinical use. One possibility is to combine the nrTMS mappings with DTI FT during the stimulation sessions to clarify possible routes for the spreading effects. Imaging of the white matter tracts may also be useful for optimizing nrTMS coil location and orientation for maximum stimulation of a predetermined axon bundle (Nummenmaa et al. 2014). Furthermore, nrTMS–EEG may provide useful information about the modifications of brain oscillations induced by nrTMS; source localization is, however, difficult (e.g., Litvak et al. 2007). Nearly simultaneous MEG–rTMS appears to be possible by a device harboring optically pumped magnetometers and rTMS coils (Okada and

Knappe, pers. comm.). These devices may produce new possibilities to probe the electrophysiological mechanisms of inducing language impairments by nrTMS.

8.5 Conclusion

Mapping language representations with nrTMS combined with video recordings for post hoc analysis appears to be a useful tool in basic research and particularly in preoperative planning of brain surgery. In our experience, it helps in surgical planning and eases the evaluation of the need of intraoperative electrophysiology. It may also shorten the duration of awake craniotomies by guiding the search of positive sites and the evaluation of the required stimulation current in DES. It also focuses skull opening, resulting in smaller craniotomies. The language-negative sites are also valuable in planning surgery, as they limit the area tested by DES during awake craniotomy. Though the first operations using only nrTMS language mapping to localize language representations have reported favorable results, its use without intraoperative awake mapping should be limited to very few selected patients who have, for example, severe psychological contraindications against awake surgery. DES during awake craniotomy is still the gold standard for cortical and subcortical functional localization in perisylvian neurosurgery. The liberal use for nrTMS language mapping in patients with tumors in the left perisylvian region and in the vicinity of the main language tracts is warranted. Particularly, left-handed patients with right-sided tumors or patients with tumors outside of the classical language areas who present with previous or transient clinical signs of language disruption probably benefit from preoperative nrTMS language mapping.

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The Use of nrTMS Data for Tractography of Language Networks

9

Gord von Campe and Margit Jehna

9.1 Introduction

From the groundbreaking works of Broca (1861), Wernicke (1874), Brodmann (1909), and Penfield and Jasper (1954), functional brain organization has traditionally been represented in a somewhat "fixed" topological fashion, with specific tasks or functions associated with discrete cortical brain areas. If some of these concepts still partially hold true today (e.g., central motor and somatosensory cortices), recent conceptual and methodological advances have shown that language organization in particular appears to be much more complex, involving several cortical areas and intervening white matter tracts, leading to a more hodotopic or "networked" model (Catani 2007; Duffau 2008, 2010). Furthermore, brain plasticity, as can be induced by slow-growing pathological processes, leads to considerable inter-patient and over time even intra-patient variability. This has important surgical implications, as disregarding any part of the language network might cause unexpected results, with potentially irreversible neurological deficits (De Benedictis and Duffau 2011).

DES has established itself as the gold standard for intraoperative mapping, as it enables the neurosurgeon to directly identify, in a nondestructive fashion, the functional cortical areas as well as the subcortical white matter tracts in the immediate vicinity of a pathological process (De Witt Hamer et al. 2012). In the case of language

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function mapping, this requires awake surgery, typically following the "asleep-awake-asleep" mode. Since full patient cooperation and concentration are essential for accurate mapping, the awake phase is time-limited. Several tools have been developed to facilitate preoperative planning in order to reduce the duration of this awake phase, including high-resolution MRI, fMRI, DTI, and more recently also nrTMS. An appealing special application of the latter modality in the noninvasive exploration of language networks is the possibility to generate truly functional seed points to be used in DTI FT.

9.2 Functional Magnetic Resonance Imaging

The technical details, indications, and practical applications of fMRI are described in Chap. 2 of this book. In brief, due to its high sensitivity and easy implementation, BOLD contrast, based on the magnetic properties of paramagnetic deoxyhemoglobin (dHb) as opposed to diamagnetic oxyhemoglobin (Pauling and Coryell 1936), is the most commonly used fMRI modality today, as it is easy to implement and does not require the administration of any exogenous contrast agent. The activation clusters, commonly overlaid on individual high-resolution structural MRI, are the result of complex statistical analyses approximating the signal changes induced by local dHb level changes (in response to specific tasks or stimuli) as a surrogate marker to an apparent "neural activity" (Ogawa et al. 1990; Kwong et al. 1992). Therefore, fMRI is able to show related cortical areas for a given task but cannot reveal the ones that are absolutely essential and would therefore need to be preserved at all costs. Also, no information is obtained regarding the white matter interconnections of these areas. The use of calculated fMRI activation clusters as seed points in DTI FT studies (see next section) has the great advantage that these can be generated in standard (high-field) MRI scanners, are quickly and readily available (once a fMRI routine has been implemented), and can often cover several different functional CNS systems (e.g., motor, somatosensory, visual, auditory, language—given appropriate study paradigms). However, since DTI FT is itself based on mathematical algorithms, this can lead to further imprecision in the exploration of white matter tracts.

9.3 Diffusion Tensor Imaging and Fiber Tracking

In view of the complex hodotopic language organization, maintaining functional language integrity can only be achieved if *both* the cortical and subcortical structures are identified and spared. Since, as already mentioned, fMRI only provides surface information, other techniques are necessary for the exploration of the subcortical brain connections: among those, DTI tractography is the most frequently used, as the required dataset can be obtained at the same time as the fMRI study. Chap. 6 deals with nTMS-based tractography of the CST and also provides additional technical aspects of DTI itself as well as nTMS-based DTI FT.

Diffusion is the process of random molecular motion by which there is a net movement of molecules from one region to another. In MRI, the main molecule of interest is

water. Random water movement is said to be isotropic, whereas directed water movement is called anisotropic. Using a specific tissue water diffusion rate sensitive sequence—DWI—Moseley et al. (1990) demonstrated that water in the CNS white matter has a highly anisotropically restricted motion, probably due to the hydrophobic nature of the myelin sheaths of the axonal tracts. DWI has since then been the elementary imaging procedure in all diffusion studies, whereas "tractography" refers to a specific mathematical modeling of the DWI dataset.

FT starts with the mathematical estimation of the diffusion tensor from the eigenvectors (direction of diffusion) and eigenvalues (strength of diffusion) in every voxel of the DWI dataset, resulting in one major diffusion direction for each voxel (Basser et al. 1994). The differences in anisotropy across space (strength or degree of anisotropy) are referred to as FA, often represented as a two-dimensional (2D) grayscale scalar map. Diffusion directional information can be color-coded, resulting in a 2D color map (DEC), conventionally using the following coloring scheme: red if the main diffusion is along the x axis (left ↔ right), green if it is along the y axis (anterior ↔ posterior), and blue if it is along the z axis (superior ↔ inferior). Tract reconstruction through propagation (FT *per se*) from the above estimated diffusion tensors, using either a deterministic or probabilistic streamline algorithm, finally results in a 3D representation of the white matter tracts. To avoid propagation into voxels possibly not belonging to the tract being reconstructed, termination criteria like defining a minimal FA threshold (to prevent tracking outside white matter regions) and/or a turning angle threshold (to prevent unrealistic fiber bending) are used (Soares et al. 2013).

Although whole-brain tractography is feasible, of special practical value for the preoperative planning is the study of white matter tracts in the immediate vicinity of, and connecting functional areas around, the pathology to be removed. This can be achieved through the process of seeding, wherein propagation is limited to only certain fibers or subfibers by using seed points in a particular ROI. The definition of these ROIs can be based on purely anatomical landmarks or derived from functional data (e.g., fMRI, MEG, nrTMS). In view of the large interindividual variability and complexity of language networks, there is a clear advantage in using functional data rather than general anatomy-based landmarks as seed points (Negwer et al. 2016a). Furthermore, it is expected that using truly functional seed points, directly generated by nrTMS (as opposed to calculated ones), will improve not only the accuracy but also the resolution of the resulting DTI tractography at the individual level as it is also described in Chap. 6 for the CST (Weiss Lucas et al. 2017).

9.4 Navigated Repetitive Transcranial Magnetic Stimulation

As outlined in Chap. 8, nrTMS is able to noninvasively map cortical language functions (Espadaler and Conesa 2011; Tarapore et al. 2013). It has a high spatial resolution, with direct electrophysiological targeting of cortical cells of every layer, and some publications correlating nrTMS language mapping with DES already exist (Picht et al. 2013; Krieg et al. 2014). It is not meant as a competition but rather as a

complement and enhancement to routine fMRI and DTI FT. As of this writing, only a few reports are available on the special use of nrTMS to generate seed points for DTI FT in functional language explorations (Negwer et al. 2016a, b; Sollmann et al. 2015, 2016; Raffa et al. 2016).

This chapter therefore demonstrates how nrTMS-based DTI FT can be used clinically according to our experience and our own protocol and furthermore provides an overview on other published protocols as well as limitations of this technique.

9.5 Methods

The workflow is based on a preoperative workup and includes the acquisition of high-resolution reference images, language-specific fMRI, DWI, nrTMS, and DTI FT. Different seed points are used, such as anatomical landmarks, fMRI activation clusters, and language-positive nrTMS stimulation points.

9.5.1 Functional MRI

At first, structural images are obtained in a MAGNETOM Prisma 3.0 T scanner (Siemens Healthcare GmbH, Erlangen, Germany), including a T1-weighted 3D MPRAGE sequence with a 1 mm isotropic resolution (1 mm^3 voxels) and the following parameters: repetition time = 1900 ms, echo time = 2.2 ms, inversion time = 900 ms, flip angle = 9°, number of slices = 176, acquisition time = 3:25 min, and a matrix size of 256 × 256. These images serve as the common reference exam for all coregistrations, for nTMS/nrTMS (and if applicable intraoperative) neuronavigation, and as anatomical background for the processed fMRI and DTI datasets. Acquisition of fMRI data is performed in the same scanner using a single-shot gradient-echo echo-planar imaging sequence (repetition time = 2500 ms, echo time = 35 ms, flip angle = 90°, matrix size = 64 × 64, resolution = 3 × 3 × 3.6 mm). The following test paradigms are used: a silent object naming task (naming on visual picture presentation), a silent sentence generation task (sentence generation on visual noun presentation), and simple motor tasks to evaluate movements of the fingers, toes, and tongue. The paradigms were chosen for their easy implementation and high interindividual reproducibility. Statistical image analysis is done with the help of the FEAT tool from the free FSL software package (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki, FMRIB, Oxford, United Kingdom) (Jenkinson et al. 2012). The statistical images are first thresholded by $z = 3.1$ with a cluster significance threshold of $p = 0.01$. After analyzing the fMRI paradigms separately, the resulting statistical images are integrated into a single combined statistical analysis to generate one functional image for the language network. For the combined analysis, 3D cope images from the separated first-level analyses are fed into one higher-level analysis using a fixed effects model. These images are thresholded at $z = 7$ with a corrected significance threshold of $p = 0.01$.

9.5.2 The Used nrTMS Setup

In our institution, the hardware setup for nrTMS consists of a MagPro X100 magnetic stimulator (MagVenture A/S, Farum, Denmark) connected to a Localite TMS Navigator (Localite GmbH, Sankt Augustin, Germany) with a Polaris Spectra infrared tracking camera (NDI, Waterloo, Canada). In order to enable precise placement of the magnetic coil over the cortical areas of interest and record the various stimulation points, high-resolution structural images obtained as detailed above are imported into the TMS navigation system and registered to the subject's head position. The (theoretical) center of stimulation is automatically extrapolated from the coil position and projected onto the cortical surface at an angle of 90° by the navigation software. Initially, single-pulse nTMS is used to determine 90% of the active motor threshold (aMT) recorded from the right APB, which is then used for the continuous TBS paradigm; 110% rMT is obtained from the same muscle. The aMT is defined as the minimum stimulus intensity that elicits a MEP response of >100 μV during moderate spontaneous background muscle activity (~10% of the maximum voluntary contraction) in at least five of ten consecutive trials. A figure-of-eight coil (C-B60, MagVenture) with two 75 mm diameter loops is placed tangentially to the scalp over the motor area at an angle of 45° to the midsagittal plane with the handle pointing laterally and posteriorly, thus generating an anteroposterior current direction in the brain. EMG recording from the right APB muscle is obtained using surface electrodes in a belly-tendon montage, and nTMS intensity is reduced gradually until aMT and rMT are reached. For the nrTMS paradigm, a different figure-of-eight coil (MCF-B65, MagVenture), also with two 75 mm diameter loops, is used. For continuous TBS the intensity is set at the individual aMT (90%) and is delivered in a burst of 3–5 pulses at a frequency of 60 Hz, repeated at a frequency of 5 Hz. The coil is always held perpendicular to the targeted cortical area. A biphasic waveform is used for both nTMS paradigms, and the subjects wear earplugs so as not to be distracted by the noise of the stimulator and to avoid nrTMS-related hearing impairment.

The same standardized object naming task (Boston Naming Test, BNT), consisting of 60 pictures, is used during preoperative nrTMS and, if applicable, intraoperative DES (Kilbride 2013). A baseline naming task is first performed and any picture that cannot be fluidly named or correctly identified is discarded. When naming the pictures, the subject has to use the phrase "this is a …" (in the mother tongue) in front of the object's name. During nrTMS, the pictures are shown using the Presentation stimulus delivery program (Neurobehavioral Systems Inc., Berkeley, USA) running on a laptop computer. The appearance of the pictures is synchronized and phase-locked to the frequency and IPI of the stimulation (PTI = 0 ms). Synchronization during intraoperative DES is achieved by means of an audio signal produced when the picture appears on the screen, and every stimulation site is tested three times in a grid-like fashion. A site with a positive response in at least two out of three stimulations is considered positive. For each stimulated site, the following possible responses are recorded: A, no response (speech arrest); B, hesitation; C, circumlocution; D, semantic paraphasia; E, phonological paraphasia; F, neologism; and G, normal

response. To minimize discomfort due to repeated nrTMS stimulations, only three pictures are presented for each stimulated site during the nrTMS session.

At the end of the nrTMS session, the recorded language-positive stimulation points (responses A–F) are verified for accuracy, converted to 5 mm spheres, and exported as regular DICOM images for further use. Given the coregistration to the high-resolution structural images, these datasets can be directly used in the DTI tractography software and, if applicable, loaded into the intraoperative neuronavigation system (StealthStation® S7, Medtronic Navigation, Coal Creek Circle Louisville, CO, USA) for validation by DES.

9.5.3 Diffusion Tensor Imaging

DWI is acquired during the same fMRI session in the same MAGNETOM Prisma 3.0 T scanner using a multiband echo-planar imaging sequence with the following parameters: repetition time = 2550 ms, echo time = 89 ms, 81 slices with a slice thickness of 2 mm, matrix size = 96 × 96, isotropic voxel size of 2 mm, b value = 1005 s/mm^2, 70 gradient directions with 9 $b = 0$ images, FA = 78°, multiband acceleration factor = 4, averages = 1, and total acquisition time = 6:32 min. The data quality is visually checked to avoid major artifacts and/or distortions due to head motion. Preprocessing of the DWI dataset includes eddy current and motion corrections, diffusion tensor estimation, and 2D reconstruction of the scalar maps.

Fiber reconstruction is done with the help of the free DSI Studio software package (http://dsi-studio.labsolver.org, Fang-Cheng Yeh, Department of Neurological Surgery, University of Pittsburgh, Pittsburgh, USA). The DTI FT algorithm implemented in DSI Studio is a generalized version of the deterministic tracking algorithm that uses quantitative anisotropy as the termination index (Yeh et al. 2013). Given the difficulties in obtaining reliable nrTMS stimulation points in the temporal region due to muscle discomfort or pain interfering with language testing, tractography in our approach is restricted to the arcuate fascicle. For comparison purposes, three seeding methods are used: anatomical, fMRI based, and nrTMS-based. The anatomical ROIs are placed using the in-software implemented JHU White Matter Labels Atlas (Mori et al. 2005) and based on the methodologies published by Catani et al. (2005) and Stieglitz et al. (2012). Before using them as seed points, individual fMRI clusters are thresholded with $z = 7$ and eroded by a factor of 3 to get a mean cluster size of ~150 mm^3 each. The language-positive nrTMS stimulation points are used as is with a size of ~65 mm^3 each. In all cases, tractography is performed with an angular threshold of 40°, a step size of 1 mm and an FA threshold automatically determined by the DSI Studio software. The number of calculated tracts was arbitrarily limited to 50,000.

9.6 Illustrative Cases

The provided illustrative cases demonstrate the strengths and weaknesses of the different used approaches.

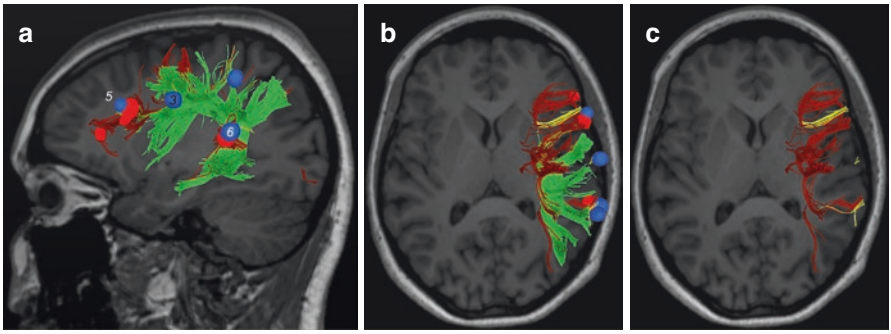

Fig. 9.1 Case 1 with three different types of seed points in a healthy volunteer. Composite image showing the result of DTI FT using three different types of seed points: anatomical in *green*, fMRI-based in *red*, and nrTMS-based in *yellow* (colors are randomly chosen without directional color-coding). The *red 3D objects* represent the fMRI activation clusters and the *blue spheres* the language-positive nrTMS stimulation points. (**a**) Sagittal view, (**b**) axial view, and (**c**) axial view showing only the fibers generated from functional seed points (fMRI and nrTMS). The numbers are related to the text

9.6.1 Case 1

Here, we present a 22-year-old right-handed healthy volunteer female, who is left language dominant. Fibers could be successfully generated using all three types of seed points (anatomical, functional fMRI-based, and functional nrTMS-based). As expected, the amount of resulting fibers decreased with decreasing ROI size (Fig. 9.1).

Using language-positive nrTMS stimulation points as ROIs revealed new fiber bundles not always visible in the anatomical or fMRI-based approach. This was especially true in the areas of the IFG (Fig. 9.1a: stimulation point number 5—speech arrest) and precentral gyrus (Fig. 9.1a: stimulation point number 3—speech arrest; small horizontal fiber bundle joining the anatomically determined arcuate fascicle), to a fewer degree also in the area of the angular gyrus (Fig. 9.1a: stimulation point number 6—less pronounced speech arrest).

9.6.2 Case 2

In this case, a 54-year-old right-handed female, who is left language dominant, suffers from a left opercular LGG. Despite the presence of the tumor mass, fibers could again be successfully reconstructed using all three types of seed points (anatomical, functional fMRI-based, and functional nrTMS-based) (Fig. 9.2). Here too, the amount of resulting fibers decreased with decreasing ROI size. DTI FT using anatomical ROIs already showed the close proximity of the arcuate fascicle along the medial aspect of the tumor (Fig. 9.3a). Using nrTMS, two clearly language-positive

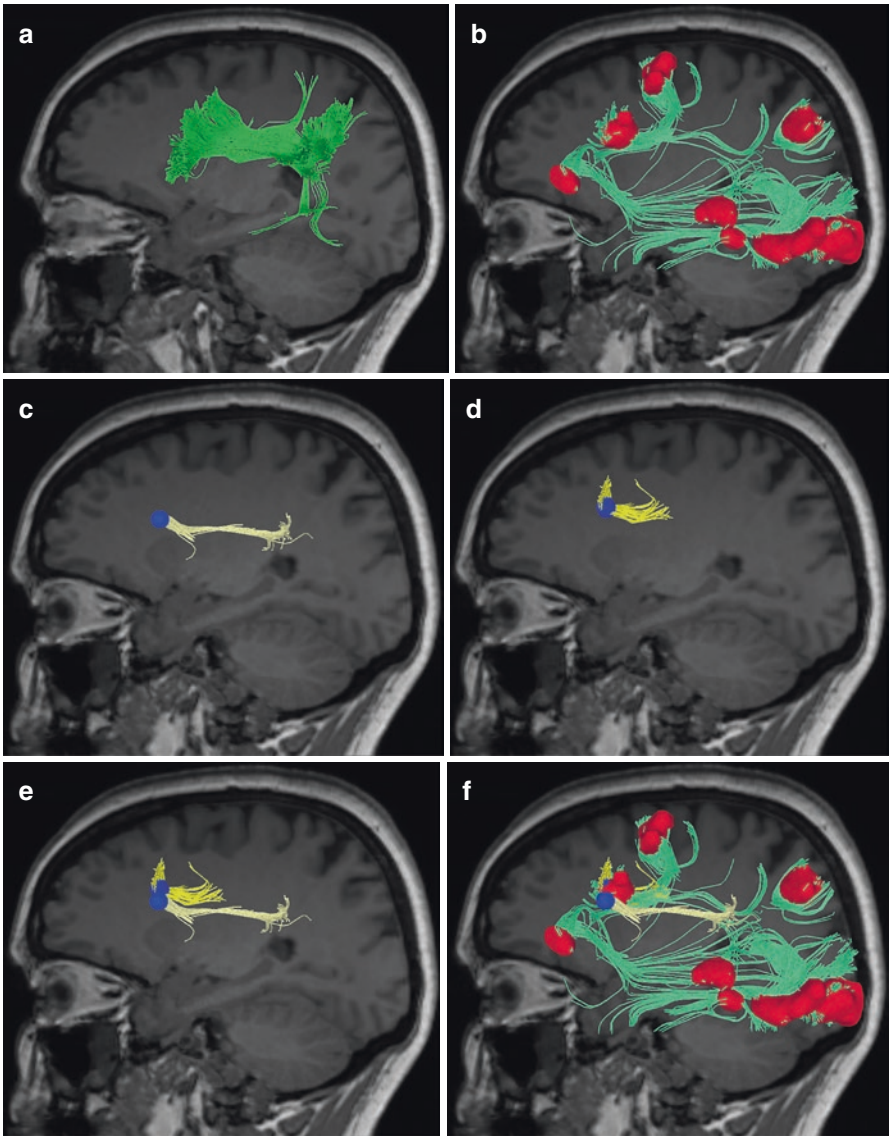

Fig. 9.2 Case 2 with three different types of seed points in a LGG patient. Composite sagittal images showing the result of DTI FT using three different types of seed points: anatomical in *green*, fMRI-based in *emerald*, and nrTMS-based in *yellow* and *beige* (colors are randomly chosen without directional color-coding). The *red 3D objects* represent the fMRI activation clusters and the *blue spheres* the language-positive nrTMS stimulation points. (**a**) Arcuate fascicle reconstructed using anatomical ROIs, (**b**) fibers generated by using fMRI-based seed points, (**c**) nrTMS stimulation point number 5 and resulting fiber bundle, (**d**) nrTMS stimulation point number 8 and resulting fiber bundle, (**e**) combined fiber bundles from **c** and **d** (language-positive nrTMS stimulation points 5 and 8), and (**f**) composite image of all fiber bundles obtained by using functional ROIs (fMRI and nrTMS)

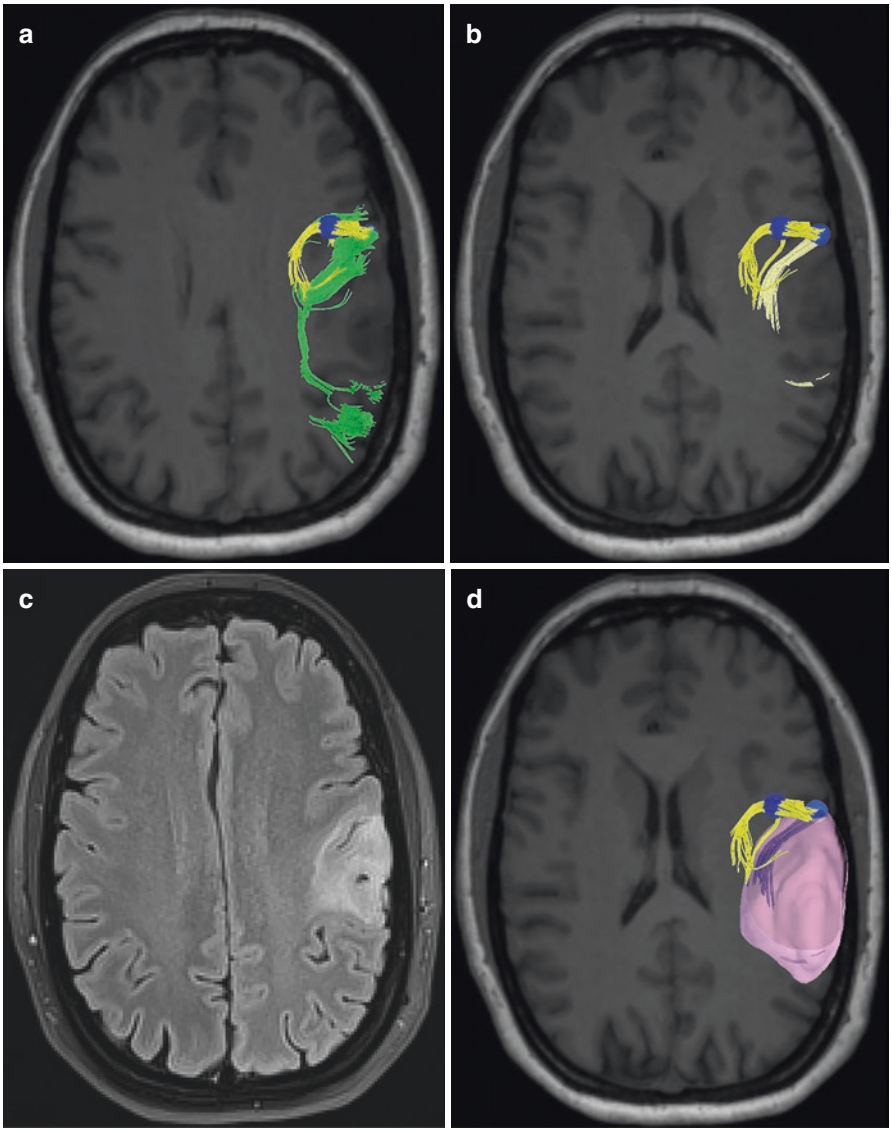

Fig. 9.3 Case 2. Arcuate fascicle reconstructed by different seed points. (**a**, **b**, **d**) Composite axial images showing the relationship between the arcuate fascicle reconstructed using anatomical seed points (in *green*), individual fiber bundles generated using nrTMS-based seed points (*yellow* and *beige*; seed points as *blue spheres*), and the left perisylvian tumor (as segmented *3D pink object*). (**c**) Axial FLAIR MR image showing the anatomical location of the left opercular tumor as a hyperintense signal alteration

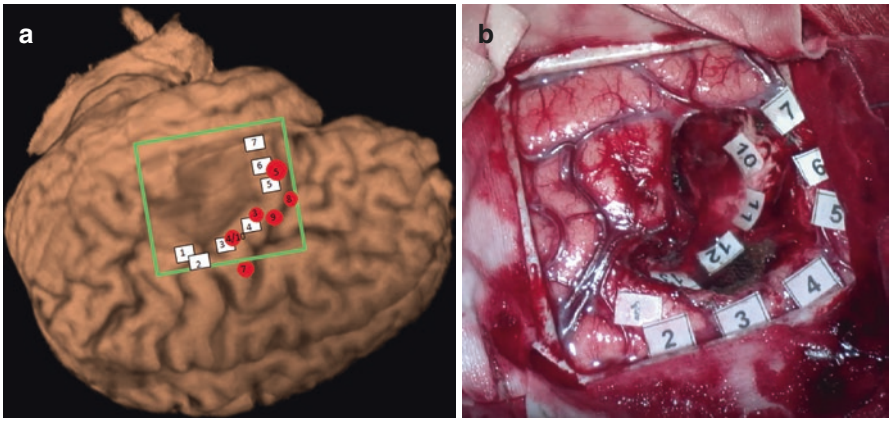

Fig. 9.4 Case 2. Comparison to intraoperative DES mapping. (**a**) A 3D brain reconstruction obtained from the high-resolution structural dataset, showing the location of the left perisylvian LGG as well as the nrTMS stimulation points (numbered *red dots*) and intraoperative DES points (numbered *white squares* matching the image on the right). (**b**) Intraoperative view after resection of the tumor and showing the various DES points (Montage courtesy of Sascha Freigang)

stimulation points (numbers 5 and 8—speech arrest; Fig. 9.4) could be identified in the precentral gyrus, superior and dorsal to the pars opercularis, in close relation to the anterior part of the tumor (Fig. 9.3b, d). Even more interesting were the detailed fiber bundles resulting from the use of these nrTMS stimulations points, which were only partially evident when using anatomy- or fMRI-based seed points. As the patient went on to have awake surgery, these results could be verified by DES (Fig. 9.4): there was a clear speech arrest when stimulating the area covered by labels 5 and 6 (matching nrTMS stimulation points 5 and 8) and articulatory motor disturbances when stimulating the area covered by labels 3 and 4 (matching motor-positive nTMS stimulation points 3, 4, and 10).

The fiber bundles revealed by using nrTMS stimulation points 5 and 8 were also confirmed intraoperatively by subcortical electrical stimulation of the area covered by labels 11 and 12 (hesitation and speech arrest). The awareness and sparing of these important interconnecting structures enabled a function-guided tumor resection without inducing any permanent postoperative motor or language deficits, all the while keeping the time necessary for the awake part of the surgery as short as possible.

9.7 Discussion

Technical details of all currently published and routinely used protocols for nrTMS-based DTI FT of language networks are summarized in Table 9.1. Despite using yet another protocol, including different hard- and software, we were able to obtain very comparable results. Given the “pinpoint” approach of nrTMS, it is no surprise

Table 9.1 Summary of various protocols for nrTMS-based DTI fibre tracking of language networks as published in the literature

Study	DTI acquisition	DTI fibre tracking parameters			Seeding ROIs		Software
		MFL	Angulation threshold	FA threshold	Anatomical/fMRI	nrTMS	
Stieglitz et al. (2012)	42 directions (b value = 1300 s/mm^2)	50 mm	Not given	0.20 (0.15 if edema)	Three anatomical: opercular part of the left-sided IFG and inferior part of the praecentral gyrus, white matter between the supra-marginal gyrus and the lateral ventricle, superior to the posterior halves of superior and medial temporal gyri	Not applicable	Brainlab iPlan 2.6/3.0
Espadaler and Conesa (2011)	Not given	Not given	Not given	Not given	Not given	Not given	Dextroscope
Sollmann et al. (2015)	15 directions (b value = 800 s/mm^2)	100 mm	>30°	0.20	None	All language-positive spots (each enlarged by 5 mm)	Brainlab iPlan 3.0.1
Negwer et al. (2016a)	6 or 15 directions (b value = 800 s/mm^2)	50 mm	>30°	0.20 (0.15 if edema)	Three anatomical: opercular part of the inferior frontal gyrus, inferior part of praecentral and supramarginal gyrus, superior and medial temporal gyrus	All language-positive spots (each enlarged by 5 mm)	Brainlab iPlan 3.0

(continued)

Table 9.1 (continued)

Study	DTI acquisition	DTI fibre tracking parameters			Seeding ROIs		Software
		MFL	Angulation threshold	FA threshold	Anatomical/fMRI	nrTMS	
Negwer et al. (2016b)	6 or 15 directions (b value = 800 s/mm^2)	40–100 mm (in 10 mm steps)	>30°	0.01–0.50 (in 0.05 steps)	None	All language-positive spots (each enlarged by 5 mm)	Brainlab iPlan 3.0
Sollmann et al. (2016)	6 directions (b value = 800 s/mm^2)	110 mm	>30°	Variable	None	All language-positive spots (each enlarged by 5 mm)	Brainlab iPlan 3.0.1
Raffa et al. (2016)	20 directions (b value = 1000 s/mm^2)	Not given	Not given	0.14–0.22	Anatomical (various)	All language-positive spots (together and singularly)	Brainlab iPlan 3.0.1
Own protocol	70 directions (b value = 1005 s/mm^2)	8 mm	40°	~0.11	Anatomical (atlas-based) fMRI (singularly, ~150 mm^3)	All language-positive spots (singularly, ~65 mm^3 each)	DSI Studio(2016-07-10 build)

The protocol by Stieglitz et al. (*first row*) only uses anatomy-based seed points and is included in the table as it serves as technical reference for language-specific tractography

that the use of these language-positive stimulation points as seed points in DTI tractography enables the visualization not merely of macroscopical white matter tracts but rather of fiber bundles and even fascicles. The same protocol was used in both, patients and healthy volunteers, and yielded the same results. Therefore, nTMS/nrTMS appears to be very similar to DES in being mostly unaffected by a tumor mass or surrounding edema (vs. possible signal loss in fMRI).

A nontrivial limitation of the software solution we used is the fact that the program itself determined the "ideal" FA threshold. Negwer et al. (2016b) have shown that this is an important parameter influencing not only the resolution of the tractography but also the number of tracts generated. Thus, the FA threshold should be individually determined by trial and error, and not automatically, even if the functional pertinence and "reality" of these appearing and disappearing fiber bundles still have to be further verified by intraoperative subcortical electrical stimulation.

Function sparing is of paramount importance in neurosurgery, as permanent neurological deficits will clearly have a negative impact on outcome. Thorough preoperative planning aims at minimizing this risk and, in case of awake surgery, at reducing the time required for intraoperative cortical and subcortical mapping. Preoperative assessment commonly involves fMRI and DTI FT. The fMRI technique yields statistically generated activation maps, the resulting cortical clusters being only an indirect representation of the underlying neural activity. DTI FT also relies on mathematical modeling of the underlying DWI dataset. The resolution and accuracy of the resulting tractography can be heavily influenced by the choice and placement of ROIs and seed points. Recently, Negwer et al. have shown that function-based ROIs (derived from functional data, e.g., fMRI, MEG, nrTMS) are to be preferred to anatomy-based ones (derived from predefined anatomical landmarks) (Negwer et al. 2016a). The focused language-positive stimulation points generated by nrTMS reflect a direct cortical inhibition and are therefore truly functional. The use of these as seed points in DTI FT comes as a clear advantage in the exploration of highly functional and complex organized networks as are the language pathways.

Despite its advantages mentioned above, nrTMS also has its shortcomings. For one it is not as readily available as fMRI, since new hardware and skilled personnel expertise is required to reliably and successfully accomplish noninvasive language mapping with nrTMS. For the other it can elicit muscle discomfort or even pain, especially if mapping is performed in the temporal region. Indeed, repetitive stimulations can induce tetanic muscle contractions (masseter and/or temporalis muscles) and/or nerve pain (facial and trigeminal nerves). Despite their benign nature, both these symptoms will interfere with reliable language assessment, so that dependable language network exploration using nrTMS is better limited to the frontoparietal region in some patients.

9.8 Conclusion

Language-positive nrTMS stimulation points can be used as valid functional seed points for DTI FT of language-specific networks. The resulting tractography appears spatially enhanced by revealing possible new subsystems in the already complex

language organization, but their exact functional relevance will require further electrophysiological confirmation. Despite a different hardware setup and somewhat customized protocol, it was still possible to obtain very comparable results to the few found in the current literature on the particular use of nrTMS in language-related tractography, highlighting the overall robustness of the procedure.

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Risk Stratification by nrTMS Language Mapping

10

Florian Ringel

10.1 Introduction

The resection of brain lesions within regions of highly functional brain is a major challenge in neurosurgery. While number one priority in cases of eloquently located lesions is the preservation of the patients' functional integrity, the achievement of a maximum safe resection needs to be fulfilled especially in oncological cases. Generalized functional anatomy was used to guide resections in or adjacent to functional areas in previous times, but the availability of intraoperative DES and identification of individual functional anatomy are used in modern neurosurgery to achieve maximum resection with functional preservation (Hervey-Jumper et al. 2015; Ojemann and Whitaker 1978; Sanai et al. 2008). In addition to many individual studies, a recent meta-analysis could clearly demonstrate that the use of intraoperative electrical, cortical, and subcortical mapping and monitoring of functional cortex and subcortical white matter tracts allows for a higher number of GTR while maintaining functional integrity of the patient (De Witt Hamer et al. 2012). Presently, the use of intraoperative DES mapping is regarded as a standard tool to identify relevant functional cortex during resections of eloquently located lesions. However, in order to allow mapping and monitoring of higher cortical functions as language, awake surgery is mandatory. These awake craniotomies have been popularized in recent years and increased the safety of surgery in functional brain areas. But, prior to the intraoperative identification of relevant functional brain structures, a preoperative identification of functional anatomy is demanded in order to evaluate the surgical risks and allow for preoperative risk stratification. Factors, such as resectability, planned EOR, the surgical approach, preoperative awareness of eloquent cortex at risk, and the identification of starting points for intraoperative stimulation, could contribute to the

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decision for resective surgery, preoperative patient counseling, intraoperative safety, and the reduction of awake time. Furthermore, while awake surgery is possible for the majority of patients, a subgroup of patients is not amendable for awake language mapping or fail language mapping during surgery (Milian et al. 2014; Nossek et al. 2013; Picht et al. 2013; Sanai et al. 2008). For this smaller subgroup of patients, presurgical mapping of language areas would be especially helpful and allow for safer asleep resections of otherwise unresectable lesions.

The most commonly used technique to provide preoperative insights in individual functional anatomy is fMRI. However, especially in the vicinity of intrinsic brain tumors, fMRI language mapping can be associated with false-negative results, thereby making fMRI language mapping unreliable for brain tumors located in language-eloquent brain areas (Giussani et al. 2010). As elaborated in previous chapters, nrTMS allows for presurgical identification of language areas in a noninvasive manner and could serve as a valuable technique for preoperative risk stratification prior to awake surgery or allow surgical resection of language-eloquent lesions in patients not amendable to awake surgery.

The feasibility of nTMS motor mapping has been evaluated nicely in a previous study revealing that in 27.4% of cases presurgical nTMS motor mapping had an objective benefit and in 54.8% an impact on the surgical resection of motor eloquent lesions (Picht et al. 2012). This highlights the influence of nTMS motor mapping in risk stratification of motor eloquent lesions.

The present chapter aims to summarize the potential influence on risk stratification of presurgical nrTMS language mapping for lesions located in or adjacent to language-eloquent cortical areas. Therefore, the topics (1) identification of hemispheric language dominance, (2) reliability (sensitivity and specificity) of nrTMS language mapping, (3) spatial resolution of nrTMS language mapping, and (4) evaluated benefits of nrTMS language mapping are elaborated in the following regarding its benefit for presurgical risk stratification.

10.2 Identification of Hemispheric Language Dominance

The classical concept of cortical language representation localized language function to the dominant hemisphere, which is the left-sided in the majority of individuals. However, several studies could identify cortical regions within the nondominant hemisphere participating in language function. Right-hemispheric language function has been identified in healthy participants as well as in left-hemispheric stroke or tumor patients by a variety of techniques (Baum et al. 2012; Baumgaertner et al. 2013; Brennan and Pylkkanen 2012; Briganti et al. 2012; Devlin and Watkins 2007; Schuhmann et al. 2012; Thiel et al. 2005; Vigneau et al. 2011). The right-sided IFG was shown to contribute to language function in a study using nonnavigated rTMS, which has a suboptimal spatial resolution in comparison to nrTMS (Thiel et al. 2005, 2006). The technique of nrTMS allows a superior spatial resolution, precise localization and quantification of left- and right-sided language areas and by the comparison of error frequencies a calculation of an HDR (Krieg et al. 2013).

In a recent nrTMS language mapping study, the right- and left-hemispheric distribution of language was assessed in healthy volunteers as well as in patients harboring lesions in left-sided language-eloquent cortical regions (Krieg et al. 2013). In all healthy volunteers and tumor patients, language errors were elicited upon stimulation of the right hemisphere supporting a role in language processing of the right hemisphere. In order to assess hemispheric dominance, the frequency of left- and right-sided language errors was compared calculating an HDR. The HDR is calculated by dividing the ER of the left-hemispheric through the corresponding right-hemispheric brain region. This can be the whole hemisphere, a lobe, or even a subgyrus. Thus, an HDR >1 means left-sided language dominance (according to nrTMS), while an HDR <1 means right-sided language dominance.

While a left-sided hemispheric dominance was predominant throughout patients and volunteers, there was a significantly higher rate of right-sided language regions in patients with left-sided perisylvian lesions in comparison to healthy volunteers (Fig. 10.1). These results were supported by another study comparing healthy volunteers and patients with left-hemispheric gliomas (Rosler et al. 2014). While in volunteers language errors were almost exclusively produced by nrTMS stimulation of the left hemisphere, tumor-harboring patients showed a higher ER in the right hemisphere suggesting tumor-induced language reorganization. These studies indicate a language shift toward the right hemisphere by brain plasticity induced by left-sided language-eloquent lesions reducing the left-hemispheric dominance. In consequence, left-sided language regions might become less essential with an increasing dominance of the right hemisphere. But, despite the presence of a language shift, it remains to be elucidated what extent of language shift to the right hemisphere allows sacrificing left-sided language areas during surgery while a sufficient compensation by the right hemisphere is secured. So far, these results were not validated regarding their significance by any further method to assess hemispheric dominance as Wada testing. Thereby, it remains to be elucidated whether the language shift to the right hemisphere as assessed by nrTMS in the patient group

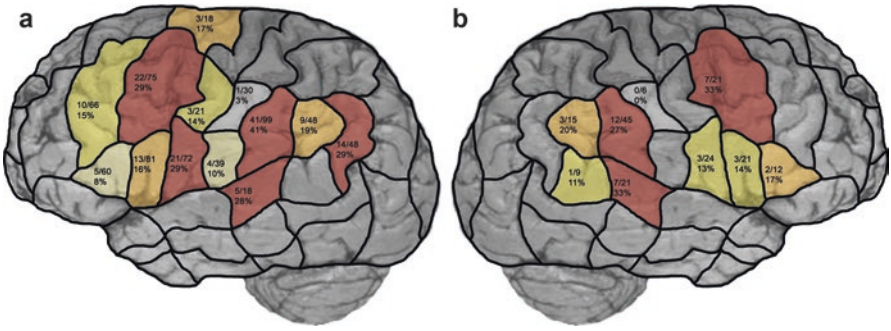

Fig. 10.1 Error rates of different brain regions. This brain template shows the ER of different brain regions (separated according to the CPS) for the left (**a**) and right (**b**) hemisphere in a patient with a left-sided angular gyrus anaplastic astrocytoma WHO° III. The ERs show that nrTMS was able to induce a considerable amount of naming errors within the right hemisphere

translates into a clinically relevant right-hemispheric compensation of left-sided language function. As an approximation to this most important question, the hemispheric language dominance as measured by nrTMS was correlated with the postoperative language outcome after resection of left-sided perisylvian lesions (Ille et al. 2016a). A significant difference of the hemispheric dominance for anterior language regions was found for patients with a new postoperative aphasia compared to patients without a new postoperative aphasia. This means patients with a shift of language function to the right hemisphere might be at lower risk for a postoperative new deficit after resection of language-eloquent regions by right-hemispheric compensation. However, the overall number of new permanent language deficits in the study was at 4%, which lowers the strength of the conclusion.

Overall, the assessment of preoperative language dominance by nrTMS might be a parameter to allow for preoperative risk assessment with respect to new language deficits. However, to further elucidate values of hemispheric dominance and the associated risk of surgery-induced deficits, studies including higher numbers of patients are necessary.

10.3 Reliability of nrTMS Language Mapping Results

The most crucial point determining the feasibility of preoperative nrTMS language mapping for risk stratification is the reliability of nrTMS-identified language-positive or language-negative areas, i.e., the sensitivity, specificity, PPV, and NPV. In order to determine these values, presurgical language mapping results were compared to the present gold standard of language mapping which is intraoperative DES during awake surgery (Fig. 10.2). As mentioned in Chap. 8, depending on the protocol of nrTMS language mapping and the algorithm of analysis of co-positive or co-negative stimulation points with nrTMS and DES, the sensitivity was 90%, the specificity 24–98%, the PPV 36–69%, and the NPV 84–99% (Picht et al. 2013; Tarapore et al. 2013). By an analysis of anterior language points surrounding Broca's area, only sensitivity and NPV were found to reach 100%. A further refinement of the protocol with regard to the timing of stimulation could even improve the NPV of nrTMS language mapping (Krieg et al. 2014). The low specificity and low PPV demonstrate that depending on the protocol of nrTMS mapping used, a high number of false-positive responses might result. In consequence, when mapping results would be used to guide the resection of a brain lesion, the false-positive points could result in a premature unnecessary termination of resection leaving potentially resectable tumor behind. However, in order to maintain patients' functional integrity, the high NPV and low number of false negative sites are important. This means the likelihood that a negatively nrTMS-mapped point was positive during surgery was 1% and thereby the reliability of a negative point is very high. Therefore, nrTMS mapping-guided resection would have a very low risk of resection of language-relevant cortical tissue if tumor in negatively mapped tissue were resected only. A resection based on nrTMS language mapping could only result in unnecessary tumor remnants but associated with a very low risk of cortical functional damage.

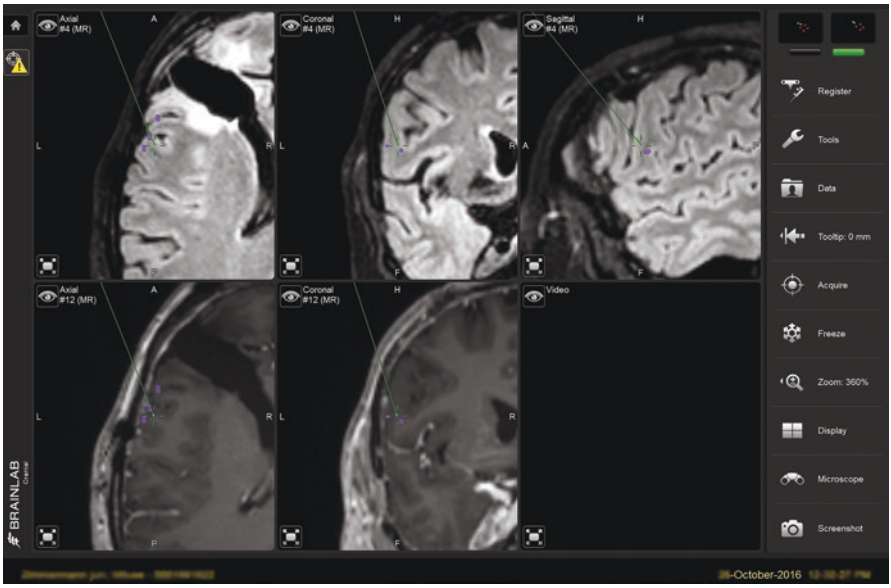

Fig. 10.2 Preoperative nrTMS language mapping vs. intraoperative DES mapping during awake surgery. This screenshot shows the intraoperative neuronavigation during awake surgery of a 21-year-old patient suffering from a recurrent opercular diffuse astrocytoma WHO° II. The preoperatively nrTMS-positive language areas (*purple*) correspond well with the intraoperative DES-positive spot identified during awake surgery (tip of the *green pointer*)

Therefore, the use of presurgical nrTMS language mapping based primarily on negative mapping results could potentially lead to a reliable estimation of resectability, corticotomy, and EOR of a language-eloquent lesion (Fig. 10.3). In cases where a lesion is surrounded by nrTMS-negative points, even resection without intraoperative electrical stimulation might be justified in patients which could not undergo awake surgery (Ille et al. 2016b). Due to the high NPV, the risk of a new postoperative deficit would be low.

10.4 Spatial Accuracy and Resolution of nrTMS Language Mapping

In addition to the predictive reliability, spatial accuracy and spatial resolution are highly important with regard to the usability of nrTMS for risk stratification. Spatial accuracy means how accurate the rTMS pulse is delivered to the stimulation spot as projected on the 3D MRI dataset in the navigation system. The spatial accuracy is composed of several factors potentially contributing to inaccuracy as optical tracking of coil localization in the navigation system, inaccuracies of head tracking, the electric field computation model, and the registration to anatomical MRIs (Chap. 1). The mean error of the real electric field hotspot to the virtual

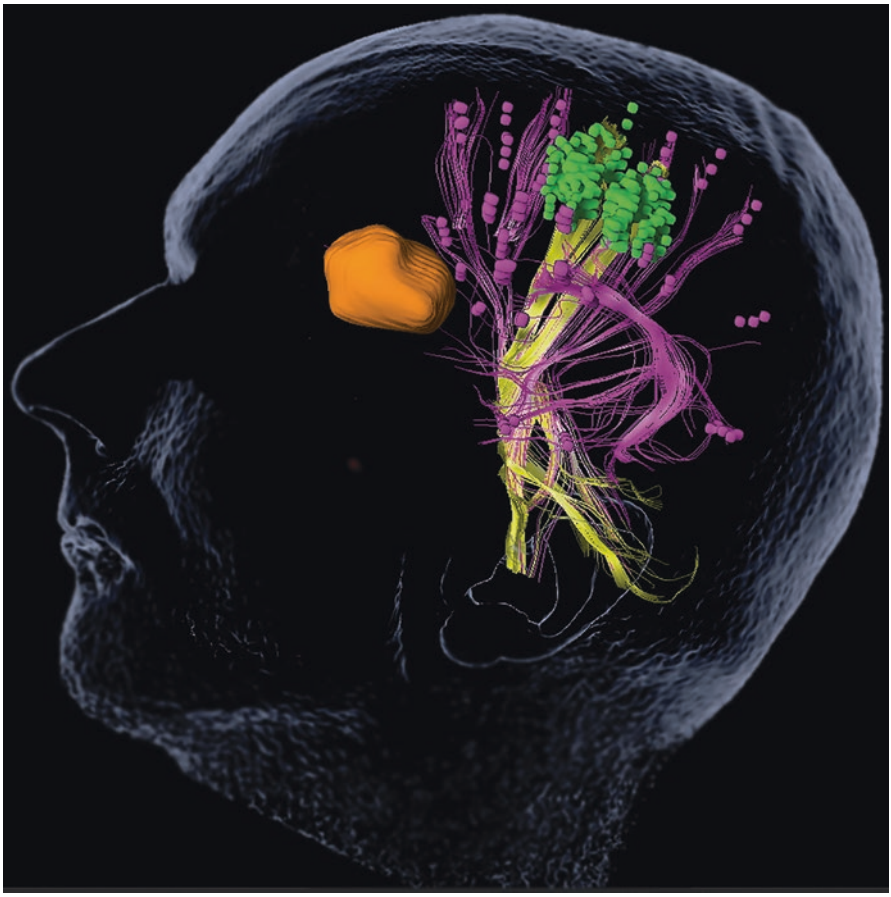

Fig. 10.3 nrTMS mapping data to confirm asleep resectability. This patient suffered from an anaplastic astrocytoma WHO° III within the triangular part of the IFG. Preoperative nrTMS language mapping of the whole left hemisphere showed that the tumor does not affect language-involved cortical or subcortical structures. Since the whole hemisphere was mapped, the cortex above the tumor can be regarded as language negative. *Orange* = tumor. *Purple* = language-positive cortical and subcortical areas according to preoperative nrTMS language mapping and nrTMS-based DTI FT of language pathways. *Green* = motor area as mapped by nTMS. *Yellow* = CST visualized via nTMS-based DTI FT

hotspot projected on the imaging dataset was calculated for a popular nTMS system to be 5.7 mm (Ruohonen and Karhu 2010) (please also see Chap. 1, Table 1). Furthermore, the spatial resolution, i.e., the minimum necessary distance of two language-relevant cortical areas that allows differentiation of these two spots, is of importance. A recent volunteer study tried to evaluate the spatial resolution by the measurement of the minimum distance necessary to discriminate a point with a low ER with a point of high ER. A mean distance of 13.8 mm was described as spatial accuracy (Sollmann et al. 2016). As the average width of a human brain

cortical gyrus is 10–20 mm, stimulation at the center of a gyrus should hit the stimulated gyrus according to the spatial accuracy, and upon stimulation of adjacent gyri, it should be possible to differentiate language function of these gyri according to the spatial resolution of nrTMS language mapping. Therefore, the technique allows for identification of language function on a gyral level, which is slightly inferior to the differentiation of approximately 5 mm of cortical DES during awake surgery. In conclusion, nrTMS language mapping allows for identification of structures at risk on the spatial level of different gyri as depicted in the CPS by Corina (Corina et al. 2010).

10.5 Clinical Benefits of nrTMS Mapping Versus No Mapping

Finally the question remains whether preoperative cortical nrTMS language mapping does translate into a clinical benefit for the patient. Aspects which might be potentially changed are indication for surgery, estimation of EOR, reduction of awake mapping time by knowledge of starting points for intraoperative DES, increased safety of asleep resections in patients where awake mapping is not feasible, and overall improved surgical outcome. However, most of these aspects have not been explicitly evaluated, so far. Whether the surgeons' knowledge of preoperative nrTMS language data do make a difference in outcome for patients undergoing resection of language-eloquent lesions using awake language mapping has been assessed (Sollmann et al. 2015). In a matched cohort analysis of 25 patients per group, the group in which presurgical language mapping results were available during surgery showed an improved language outcome and smaller craniotomies, while the EOR, overall rate of perioperative complications, and the duration of surgery did not differ. In another publication, four cases of patients with left-sided perisylvian lesions which have been resected on the basis of preoperative nrTMS language data only because they were not testable during awake surgery have been reported (Ille et al. 2016b). None of the patients had a permanent new deficit after surgery. However, although encouraging, this is nonsystematic data on the basis of cases.

10.6 Conclusion

In conclusion, nrTMS-based preoperative language mapping does allow for a subjective risk stratification since clear numbers from larger series are still pending. The risk associated with certain calculated values of hemispheric dominance needs to be clearly defined in order to allow for a clear estimation of an associated risk for new surgery-related deficits. Furthermore, additional series are needed comparing nrTMS mapping results with DES during awake surgery to assess a more robust predictive value of nrTMS language mapping in relation with hemispheric dominance. So far, nrTMS language mapping seems to be promising as a valuable tool for risk stratification after substantiation of available data.

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Part IV

Special Aspects

Mapping of Further Brain Functions

11

Sebastian Ille

11.1 Introduction

Today, all specialized neuro-oncological centers use DES to locate individual functional areas of the brain. At least for the mapping of language function, patients have to be awake during surgery (Ojemann and Whitaker 1978; Ojemann et al. 1989; Haglund et al. 1994; Sanai et al. 2008; De Witt Hamer et al. 2012).

For decades the preservatiown of the patients' motor and language function had priority over other essential brain functions. Meanwhile, specialized centers also map further essential brain functions during awake surgery, such as working memory, arithmetic processing, visuospatial functions, judgment, recognition of facial emotions, or even playing instruments and singing (Thiebaut de Schotten et al. 2005; Duffau et al. 2002; Brandling-Bennett et al. 2012; Giussani et al. 2010a; Plaza et al. 2008; Roux et al. 2009a).

Some of the abovementioned brain functions apart from motor and language function have also been examined by noninvasive mapping techniques. Arithmetic processing, for instance, was already mapped by fMRI and TMS (Cohen et al. 2000; Rusconi et al. 2005). Although replacing intraoperative awake mapping by preoperative noninvasive mapping should not be the aim in neuro-oncology, however, noninvasive techniques have advantages: they can provide us with information prior to thinking about indication of surgery at all. Moreover, they can also be performed in healthy subjects with the aim of gaining information about brain functions for basic research. This becomes important especially for brain functions, which are not standardly mapped during awake surgery. Moreover, for patients, a preoperative noninvasive mapping is performed in a more pleasant and relaxing

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environment compared to intraoperative mapping. Thus, such preoperative mapping can prepare the patient for the awake procedure, which also enables the neuropsychologist to better select the appropriate tasks and the surgeon to tailor his surgical approach before entering the operating room and serves as a backup option if awake surgery fails. Moreover, as it was observed for language mapping by nrTMS, the preoperative data allows for more targeted intraoperative DES mapping (Picht et al. 2013; Tarapore et al. 2013; Sollmann et al. 2015). Regarding the preoperative mapping technique, fMRI has shown to be less reliable in tumor patients, especially in the vicinity of lesions (McGraw et al. 2001; Ille et al. 2015; Giussani et al. 2010b). With this in mind, particularly nrTMS language mapping has shown a good correlation as compared to results obtained by DES during awake surgery as the gold standard technique, at least in terms of negative mapping (Picht et al. 2013; Tarapore et al. 2013).

The neurosurgical application of TMS significantly increased after the introduction of nTMS. However, since many studies concerning the mapping of higher cortical functions by rTMS have already been performed before the age of nrTMS, this chapter outlines stimulation protocols and test setups of both approaches: nrTMS and (nonnavigated) rTMS.

11.2 Basic Principles of Mapping Further Brain Functions

As repetitively described for language mapping by nrTMS, the mapping of further brain functions is most often conducted by stimulating with repetitive pulses while the patient or healthy subject is performing a special task.

In contrast to the application of single pulses, repetitive pulses are mostly used for the examination of higher cortical brain functions in order to induce a virtual lesion (Tables 11.1–11.4) (Pascual-Leone et al. 1991). However, the underlying mechanisms of the virtual lesion model are not yet clear (Miniussi et al. 2010). Probably, it is a combined effect of the suppression of neural signals (Harris et al. 2008) and the induction of random neural activity (Ruzzoli et al. 2010; Walsh and Cowey 2000) within the underlying cortical region, which is also depending on anatomo-functional characteristics of the tissue (Miniussi et al. 2010; Siebner et al. 2009). Up to now, the most often used stimulation frequency is 10 Hz/5 pulses (Tables 11.1–11.4).

As for language mapping, the mapping of further brain functions starts in many published protocols with the determination of the rMT via a rough motor mapping as described in Chap. 1. The stimulation intensity of the mapping can then be related to the rMT. In most cases, rTMS or nrTMS mappings are performed with a stimulation intensity of 100% rMT. In contrast, a large part of research groups does not relate the mapping intensity to the individual subject's rMT but stimulates all participants of a study with a similar intensity as defined by % of maximum stimulator output which is, unfortunately, impossible to transfer directly to other stimulators and coils (Tables 11.1–11.4). However, the intensity must be adapted to the patient's

Table 11.1 Arithmetic processing

Study	Stimulation	Frequency (Hz)	Pulses	PTI (ms)	ISI (ms)	DT (ms)	Intensity	Task	Subjects	Cases
Maurer et al. (2016)	nrTMS	5	10	0	3,000	700	100% rMT	Four basic arithmetic operations	Healthy volunteers	20
Andres et al. (2011)	fMRI-guided nrTMS	10	4	100	5,000	150	65% stimulator output	Subtraction, multiplication	Healthy volunteers	10
Cohen Kadosh et al. (2007)	fMRI-guided nrTMS	10	3	220	6,000	1,000	60% stimulator output	Numerical and physical size comparison	Healthy and dyscalculic volunteers	Five healthy/ five dyscalculic
Rusconi et al. (2005)	nrTMS	10	5	0	2,500	65	60% stimulator output	Parity- and magnitude-matching	Healthy volunteers	8
Sandrini et al. (2004)	rTMS	15	4	0	Reaction times	Reaction times	110% rMT	Number comparison	Healthy volunteers	9
Gobel et al. (2001)	rTMS	10	5	Before stimulus	Reaction times	Reaction times	105% rMT	Number classification	Healthy volunteers	6

Overview on studies investigating the mapping of arithmetic processing by TMS. DT = display time of the presented test image

Table 11.2 Visuospatial attention

Study	Stimulation	Frequency (Hz)	Pulses	PTI (ms)	ISI (ms)	DT (ms)	Intensity	Task	Subjects	Cases
Wang et al. (2016)	nrTMS	1	Continuous	0	Reaction times	Reaction times	100% rMT	Visuospatial attention shifting	Healthy volunteers	16
Wu et al. (2016)	nrTMS	1	Continuous	−3,00,000+ task	1,500	500	100% rMT	Detection	Healthy volunteers	16
Giglhuber et al. (submitted for publication)	nrTMS	5	10	0	3,000	50	100% rMT	Greyscale	Healthy volunteers	10
Giglhuber et al. (2016)	nrTMS	5	10	0	3,000	50	100% rMT	Line bisection	Healthy volunteers	10
Bagattini et al. (2015)	rTMS	1	1,800	n.s.	n.s.	n.s.	90% rMT	Line bisection + detection	Healthy volunteers	14
Studer et al. (2014)	rTMS	5	450	Before task	n.s.	350	40% stimulator output	Roulette betting	Healthy volunteers	28
Salatino et al. (2014)	TMS	Single pulse	1	150	≥4,000	50	115% rMT	Line bisection	Healthy volunteers	8
Mahayana et al. (2014b)	rTMS	10	5	0	Reaction times	200	60% stimulator output	Line bisection	Healthy volunteers	15
Plow et al. (2014)	nrTMS	1	9,00,000	Before task	n.s.	3,000	75% stimulator output	Visual tracking	Healthy volunteers	10
Mahayana et al. (2014a)	nrTMS	10	5	0	Reaction times	Individual threshold	60% stimulator output	Visual search	Healthy volunteers	24
Ricci et al. (2012)	TMS	Single pulse	1	150	n.s.	50	115% rMT	Line bisection	Healthy volunteers	3

Sauseng et al. (2011)	rTMS	1	900	n.s.	2,000–3,000	83	110% rMT	Detection	Healthy volunteers	12
Heinen et al. (2011)	nrTMS	11	3	90, 180, 270	n.s.	270	120% rMT	Detection	Healthy volunteers	12
Blankenburg et al. (2010)	rTMS	10 Hz	5	0	2,430	570	75% stimulator output	Detection	Healthy volunteers	8
de Graaf et al. (2009)	nrTMS	Triple pulse	3	Four conditions	6,000, 7,000, 8,000	300	120% rMT	Clock	Healthy volunteers	13
Oliver et al. (2009)	rTMS	10 Hz	5	−100 to 400	n.s.	Individual	100% rMT	Gap detection	Healthy volunteers	9
Van Ettinger-Veenstra et al. (2009)	fMRI-guided nrTMS	Triple pulse	3	−60, −30, 0	n.s.	120	120% rMT	Cue/postponed saccade	Healthy volunteers	10
Cattaneo et al. (2009)	nrTMS	Triple pulse	3	−500	n.s.	200	65% stimulator output	Line bisection	Healthy volunteers	9
Nyffeler et al. (2008)	rTMS	30	801	n.s.	n.s.	5,500	90% rMT	Visual exploration	Healthy volunteers	12
Sack et al. (2007)	rTMS	13.3	5	0	2,000	300	100% stimulator output	Clock	Healthy volunteers	8
Neggers et al. (2007)	fMRI-guided nrTMS	Triple pulse	3	60, 90, 120	n.s.	120	110% stimulator output	Cue/postponed saccade	Healthy volunteers	8

(continued)

Table 11.2 (continued)

Study	Stimulation	Frequency (Hz)	Pulses	PTI (ms)	ISI (ms)	DT (ms)	Intensity	Task	Subjects	Cases
Muggleton et al. (2006)	rTMS	10	5	0	Reaction times	60–260	65% stimulator output	Detection	Healthy volunteers	10
Meister et al. (2006)	TMS	Single pulse	1	150/250	3,250	40	60% stimulator output	Detection	Healthy volunteers	14
Dambeck et al. (2006)	TMS	Single pulse	1	150/250	3,210	40	60% stimulator output	Detection	Healthy volunteers	10
Hung et al. (2005)	nrTMS	10	5	0	n.s.	160	60% stimulator output	partial-/color-report control	Healthy volunteers	9
Thut et al. (2005)	rTMS	1	25 min	n.s.	n.s.	40	80% stimulator output	Detection	Healthy volunteers	10
Mevorach et al. (2005)	rTMS	1	600	n.s.	n.s.	80	90% rMT	Letters and shapes	Healthy volunteers	22
Koch et al. (2005)	rTMS	Single/paired pulse	1/2	100/150	1, 3, 5, 10	40	130% rMT	Detection	Healthy volunteers	9
Kim et al. (2005)	rTMS	10	1,000	Blocks	2,180	180	80% rMT	Line bisection	Healthy volunteers	20
Ellison et al. (2004)	nrTMS	4/10	2/5	0	4,000	Reaction times	65% stimulator output	Line bisection/visual search	Healthy volunteers	5
Chambers et al. (2004)	nTMS	Single pulse	1	30–360	n.s.	100	63% stimulator output	Detection	Healthy volunteers	3

Muri et al. (2002)	rTMS	Double pulse	2	1,20, 270, 520	3,000–5,000	120	80% stimulator output	Symbols	Healthy volunteers	10
Bjoertomt et al. (2002)	rTMS	n.s.	n.s.	0	Reaction times	200	65% stimulator output	Line bisection	Healthy volunteers	6
Hilgetag et al. (2001)	rTMS	1	600	≤3,00,000	2,250	40	90% rMT	Detection	Healthy volunteers	7
Fierro et al. (2001)	TMS	Single pulse	1	1,50, 225, 300	≥30,000	50	115% rMT	Line bisection	Healthy volunteers	10
Fierro (2000)	rTMS	25	10	0	≥30,000	50	115% rMT	Line bisection	Healthy volunteers	11
Pascual-Leone et al. (1994)	rTMS	25	5	0	100	n.s.	115% rMT	Detection	Healthy volunteers	6

Overview on studies on the mapping of visuospatial attention by TMS (n.s. = not specified; negative PTI means TMS onset prior to stimulus onset)

Table 11.3 Face processing

Study	Stimulation	Frequency (Hz)	Pulses	PTI (ms)	ISI (ms)	DT (ms)	Intensity	Task	Subjects	Cases
Maurer et al. (2017)	nrTMS	10	5	0	3,000	700	100% rMT	Famous faces	Healthy volunteers	20
Ferrari et al. (2016)	nrTMS	10	3	−200	n.s.	n.s.	60% stimulator output	Trustworthy-ness of faces	Healthy volunteers	12
Zachariou et al. (2016)	fMRI-guided nrTMS	10	5	0	4,600–5,800	500	70% stimulator output	Same-different face detection	Healthy volunteers	20
Solomon-Harris et al. (2016)	fMRI-guided nrTMS	1	1,200	n.s.	200	800	60% stimulator output	Face identity and butterflies	Healthy volunteers	13
Gamond and Cattaneo (2016)	nrTMS	10	3	0	2,700	300	60% stimulator output	Emotion recognition	Healthy volunteers	20
Bona et al. (2015)	fMRI-guided nrTMS	10	3	0	Response time	75, 500	40% stimulator output	Symmetry detection, facial features	Healthy volunteers	14
Pitcher (2014)	fMRI-guided nrTMS	10/ paired-pulse	5/2	0/20–60, 60–100, 100–140, 130–170, 170–210	1,500	250	60% stimulator output	Face identity and expression	Healthy volunteers	14
Renzi et al. (2013)	nrTMS	20	3	100	2,000	200	60% stimulator output	*Jane* faces	Healthy volunteers	16
Mattavelli et al. (2013)	nrTMS	Single pulse	1	100	1,200–1,400	700	62 ± 3% stimulator output	Face identity and expression	Healthy volunteers	11

Rochas et al. (2013)	nrTMS	10	5	0	±4,400	50	80% rMT	Facial emotion recognition	Healthy volunteers	20
Pitcher et al. (2011)	fMRI-guided nrTMS	10	5	0	1,500	250	60% stimulator output	Face orientation	Healthy volunteers	10
Mattavelli et al. (2011)	nTMS	Single pulse	1	Immediately before	n.s.	Until response	65% stimulator output	Emotion-related word and face	Healthy volunteers	20
Dzhelyova et al. (2011)	nrTMS	10	5	0	3,500–4,250	500	65% stimulator output	Sex and trustworthy-ness	Healthy volunteers	12
Kadosh et al. (2011)	nrTMS	10/ paired-pulse	5	0/130–170, 170–210, 210–250, 250–290, 290–330	Response time	Until response	60% stimulator output	Emotion recognition	Healthy volunteers	8
Pitcher et al. (2009)	rTMS	10	5	0	1,500	500	60% stimulator output	Face, body and object	Healthy volunteers	16
Pitcher et al. (2008)	rTMS	10/ paired-pulse	5/2	0/20–60, 60–100, 100–140, 130–170, 170–210, 210–250	1,500	250	60% stimulator output	Identity and expression discrimi-nation	Healthy volunteers	28

(continued)

Table 11.3 (continued)

Study	Stimulation	Frequency (Hz)	Pulses	PTI (ms)	ISI (ms)	DT (ms)	Intensity	Task	Subjects	Cases
Pitcher et al. (2007)	rTMS	10/ paired-pulse	5/2	0/20–60, 60–100, 100–140, 130–170, 170–210, 210–250	1,500	250	60% stimulator output	Face part discrimi-nation	Healthy volunteers	25
Pourtois et al. (2004)	TMS	Single pulse	1	100/200	3,250	100	110% rMT	Facial emotion recognition	Healthy volunteers	12

Overview on studies on the mapping of face processing by TMS (n.s. = not specified; negative PTI means TMS onset prior to stimulus onset)

Table 11.4 Categorization

Study	Stimulation	Frequency (Hz)	Pulses	PTI (ms)	ISI (ms)	DT (ms)	Intensity	Task	Subjects	Cases
Maurer et al. (in preparation)	nrTMS	10	5	0	3,000	700	100% rMT	Living/ non-living	Healthy volunteers	20
Jacquet and Avenanti (2015)	nTMS	Single pulse	1	0	1,000	1,500	110% rMT	Goal-/ grip-recognition	Healthy volunteers	27
Passeri et al. (2015)	rTMS	10	5	0	1,200	190	100% rMT	Verbal category membership	Healthy volunteers	18
Cattaneo et al. (2010)	nTMS	Single pulse	1	0	n.s.	Until response	65% stimulator output	Tool and animal words	Healthy volunteers	12
Fuggetta et al. (2009)	rTMS	10	5	−750	2,450	1,500	60–65% stimulator output	Picture-word verification	Healthy volunteers	9

Overview on studies on the mapping of categorization by TMS (n.s. = not specified; negative PTI means TMS onset prior to stimulus onset)

comfort on the one hand but also to the possibility of inducing specific errors on the other hand in all cases.

The use of nrTMS is strongly recommended if available. Neuronavigation enables us to better locate the stimulation sites and to analyze the mappings more precisely. Most researchers only stimulate single targets based on the results of prior studies. Of course, this is reasonable; however, this practice limits the gain in knowledge of further eloquent cortical sites. Up to know, we do not entirely understand the underlying processes of the following neuropsychological brain functions. Hence, it is recommended to also stimulate further cortical sites in order to examine these complex functions more accurately.

11.2.1 Arithmetic Processing

As examined by multiple neuroimaging studies using fMRI or PET as well as lesion-based studies, arithmetic processing was assumed to be located within the inferior parietal lobe of the dominant hemisphere (Burbaud et al. 1999; Cohen et al. 2000; Cowell et al. 2000; Dehaene et al. 1996; Hayashi et al. 2000; Lee 2000; Martins et al. 1999; Mayer et al. 1999; Zago et al. 2001). Based on the knowledge of these studies, Whalen and later Duffau were the first to ask patients with a left-sided tumor within the parietal lobe to perform arithmetic processing tasks during bipolar DES in the setting of an awake craniotomy (Whalen et al. 1997; Duffau et al. 2002). The results of Whalen et al.'s (1997) and Duffau et al.'s (2002) reports have also been reproduced and extended by DES in the last decade (Roux et al. 2003, 2009b; Kurimoto et al. 2006; Maldonado et al. 2011; Pu et al. 2011; Yu et al. 2011). Most importantly, Della Puppa et al. were even able to show the involvement of the right-sided parietal lobe in arithmetic processing by DES as well as the mapping of subcortical fiber tracts involved in arithmetic processing by subcortical DES (Della Puppa et al. 2013, 2015a, b).

Gobel et al. applied rTMS to the parietal lobe in order to show its involvement in number representation (Gobel et al. 2001). In 2004, Sandrini et al. started to examine number processing by rTMS (Sandrini et al. 2004). At this time they used a simple number comparison task and concluded that they were able to slow down the subject's number processing by applying nrTMS to the left inferior parietal lobe but not when applying it to the right. Similarly, another group applied rTMS to the left and right parietal lobe while subjects performed an addition task. They could find significantly longer reaction times during stimulations over the left but not over the right hemisphere (Gobel et al. 2006b). Also Rusconi et al. were able to disrupt number processing when applying nrTMS to the left angular gyrus in a study in which they tried to reproduce Gerstmann's syndrome (Rusconi et al. 2005). In 2007 it was shown that virtual dyscalculia is also inducible by fMRI-guided nrTMS over the right parietal lobe of healthy volunteers (Cohen Kadosh et al. 2007). Andres et al. also performed a study using a two-step approach: first they identified cortical regions within the parietal lobes involved in subtraction and multiplication by fMRI. As a second step, they stimulated these regions by nrTMS in order to induce

a virtual lesion. Their results showed arithmetic processing function in the left as well as in the right intraparietal sulcus (Andres et al. 2011).

Another nrTMS study on the cortical mapping of arithmetic processing was published in 2016 (Maurer et al. 2016). Maurer et al. performed nrTMS mappings of both hemispheres in 20 right-handed healthy subjects using a stimulation intensity of 100% rMT and a stimulation frequency of 5 Hz and 10 pulses. During nrTMS stimulations, healthy subjects performed a task with simple arithmetic operations consisting of addition, subtraction, multiplication, and division. The core result of this study is the feasibility of detecting cortical arithmetic processing function in healthy subjects by nrTMS and particularly to differentiate the location of arithmetic processing between predefined cortical subareas. Despite these promising results showing the feasibility to induce arithmetic processing errors by nrTMS in both hemispheres, they also found the highest ER for all errors in all subjects within the right-sided ventral precentral gyrus (vPrG). With this in mind, the problem of differentiating between real arithmetic processing errors and the impairment of language processing or dysarthria induced by nrTMS must be seen as a limitation or potential pitfall, despite most of the positive sites found in this study were in good accordance with current literature (Maurer et al. 2016). However, the study showed us the feasibility of mapping arithmetic processing by nrTMS and enables us to approve the results in patient studies.

Table 11.1 gives an overview of publications for the mapping of arithmetic processing by TMS. Up to now, TMS for the mapping of arithmetic processing has most often been used in healthy volunteers and by the application of different number or arithmetic processing tasks (Table 11.1). Most reported studies used 10 Hz and a short/no PTI. For its application in neurosurgery with the aim of finding eloquent regions preoperatively, the use of a task combining the four basic and easy arithmetic operations seems to be highly effective, such as $9 + 1$, $5 - 2$, 2×7, $12 / 4$ (Maurer et al. 2016).

11.2.2 Visuospatial Attention

Neglect-like symptoms and visuospatial deficits can be observed in patients who underwent resections of parietal lobe tumors (Russell et al. 2005; Hommet et al. 2004). Sanai et al. analyzed 119 cases of parietal tumor resection. They found not otherwise specified visual deficits in 9.2% (6.7% permanent deficits) and parietal lobe symptoms such as right-left confusion, finger agnosia, sensory extinction, or astereognosis in 8.4% (2.5% permanent deficits) of cases (Sanai et al. 2012). With this in mind, the feasibility of mapping visuospatial attention by DES during awake surgery has already been shown (Bartolomeo et al. 2007; Thiebaut de Schotten et al. 2005).

Visuospatial attention and its processing is based on a complex network including cortical as well as subcortical levels (Corbetta et al. 2005; Heilman 1980; Kinsbourne 1977; Lunven et al. 2015; Umarova et al. 2014; Suchan et al. 2014; Duecker and Sack 2014; Sack 2010). Most importantly, neglect or neglect-like

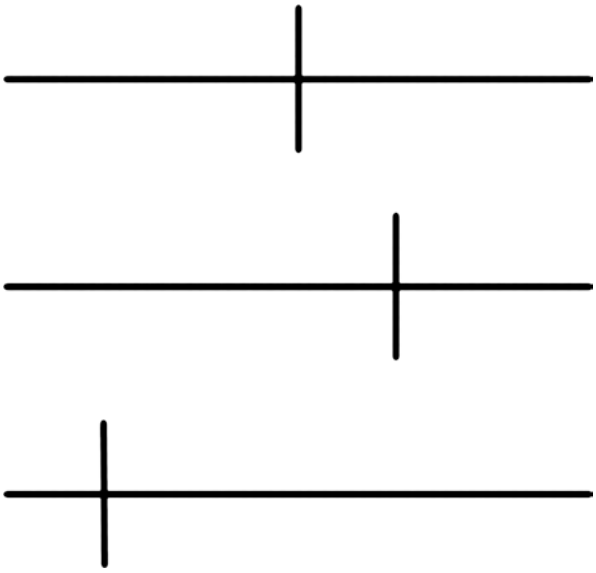

Fig. 11.1 Line bisection task. The figure shows the line bisection task. The task is designed as a horizontal line, which is bisected by a vertical landmark. The bisection can either be symmetrically with an equal length of the left and right part or asymmetrically with a longer left or right segment. Subjects are instructed to bisect the horizontal lines and to name the longer or the shorter segment (Giglhuber et al. 2016)

distortions significantly influence the postoperative functional outcome as well as the patient's quality of life (Jehkonen et al. 2000, 2006; Katz et al. 1999).

By the use of a number bisection task, Gobel et al. were able to evoke neglect-like symptoms by applying rTMS to the right-sided parietal lobe of healthy subjects. For this task, subjects have to name the midpoint of a numerical interval without the necessity of arithmetic processing (Gobel et al. 2006a). Most often, researchers use the line bisection task or detection tasks for the mapping of visuospatial attention (Fig. 11.1 and Table 11.2). The line bisection task has also been used intraoperatively (Roux et al. 2011). The task is designed as a horizontal line, which is bisected by a vertical landmark. The bisection can either be symmetrically with an equal length of the left and right part or asymmetrically with a longer left or right segment. Subjects are instructed to bisect the horizontal lines and to name the longer or the shorter segment (Fig. 11.1) (Giglhuber et al. 2016).

The feasibility of inhibiting visuospatial orientation by TMS has even been shown in animals by Valero-Cabre et al. In this sham-controlled study, they stimulated the parietal lobe of cats with a frequency of 1 Hz for 20 min. Interestingly, they also showed that the induced effects lasted for about 20 min (Valero-Cabre et al. 2006). By the measurement of eye movements during the application of TBS over the right parietal cortex, Nyffeler et al. were able to induce visual neglect-like effects in healthy subjects (Nyffeler et al. 2008). Koch et al. also used TBS, however, with another intention: they stimulated the left-sided parietal lobe in patients suffering

from hemispatial neglect due to right-hemispheric stroke. By inhibiting the hyperexcitability of the left hemisphere with rTMS, they accelerated the recovery from hemispatial neglect after 2 weeks of stimulations (Koch et al. 2012). Despite only done in three healthy subjects, Ricci et al. were able prove these promising results even for single-pulse TMS by combined TMS-fMRI sessions. They evoked neglect-like behavior by stimulating the right-sided parietal lobe. Afterward, they were able to show decreased neuronal activity within frontoparietal areas according to the results of lesion-based studies (Ricci et al. 2012). Another important study regarding the examination of visuospatial attention by nrTMS is the publication of Giglhuber et al. (2016). Visual neglect-like symptoms were observed during the stimulation with 5 Hz and 10 pulses over 52 predefined cortical sites of both hemispheres by the use of a line bisection task (Fig. 11.1). Regarding the line bisection task, the authors found significantly more rightward errors during the right-sided stimulation as well as more leftward errors during the stimulation of the left hemisphere (Giglhuber et al. 2016). This study also shows that it is crucial for TMS to select the right task suiting the TMS setup, particularly for the mapping of visuospatial attention and the induction of neglect-like effects (Bonato 2012; Coello et al. 2013). Table 11.2 provides an overview on previous studies on the mapping of visuospatial attention.

Another well working task for mapping visuospatial attention is the grayscale task. This task shows different pictures with mirrored but otherwise identical pairs of horizontal grayscales (Fig. 11.2). Subjects are asked to respond which of the two grayscales appears darker. After baseline testing, the subjects then present a known phenomenon called pseudo-neglect to the left side. In one nrTMS study, the right hemisphere showed a higher overall ER than the left hemisphere. Additionally, leftward errors were elicited by stimulations to the SFG and again posterior parietal areas, while rightward errors were evoked due to stimulation of the IFG and the TPJ (Giglhuber et al. submitted for publication).

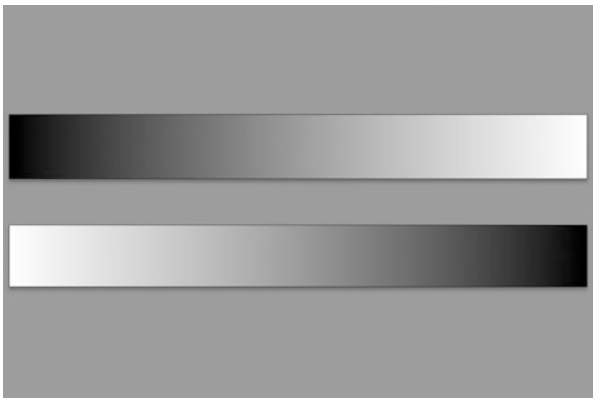

Fig. 11.2 Grayscale task. The figure shows an example for the grayscale task. This task shows different pictures with pairs of horizontal grayscales. Subjects are asked to respond which of the two grayscales appears darker. The task can be used for the mapping of visuospatial attention

As Table 11.2 shows, most researchers use the line bisection task. This task seems to be the most appropriate one for the mapping of visuospatial attention. Moreover, repetitive pulses with a frequency of 5–10 Hz and a pulse onset simultaneously to the presentation of the stimulus (PTI = 0 ms) cover the whole process of visuospatial attention. Most importantly, the DT of the stimulus presentation must be short. The use of a DT of 50 ms increases the sensitivity crucially.

11.3 Face Processing

The mapping of the cortical representation of face processing seems like a very experimental approach on the first view. However, face perception also includes subfunctions, such as the judging of emotion, identity, and trustworthiness (Atkinson and Adolphs 2011). When this brain function is disturbed by stroke or other brain lesions, it means a decrease in quality of life for patients but also their social environment and thereby justifies its mapping and preservation (Barton 2014; Busigny et al. 2014; Hier et al. 1983; Rapcsak et al. 2001; Young et al. 1993; Gainotti and Marra 2011). The underlying cortical locations of face processing as well as its subcortical network are complex. The cognitive process consists of two parts: the visual perception of faces and the matching to the face memory (Rapcsak 2003). Moreover, face processing is bilaterally located with a predominance of the right hemisphere (Gainotti and Marra 2011; Landis et al. 1986). This bilaterality of face processing and its complexity has also been demonstrated by surgical cases and intraoperative mapping (Corrivetti et al. 2016; Giussani et al. 2010a). Moreover, an anatomo-functional study examined the underlying subcortical structures on the one hand and showed the feasibility of mapping face processing during awake surgeries on the other hand (De Benedictis et al. 2014).

Concerning noninvasive modalities, face processing has already been described and visualized by fMRI (Hadjikhani and de Gelder 2002; Keenan et al. 2000; Gauthier et al. 2000; Druzgal and D'Esposito 2003; Fruhholz et al. 2011; Kitada et al. 2009). A meta-analysis combining fMRI data of healthy subjects showed involvement in face processing within the occipital, temporoparietal, and prefrontal cortex, the limbic system, and the cerebellum as well as within the according subcortical areas (Fusar-Poli et al. 2009).

Face processing has also been examined by rTMS and reported in various articles (Table 11.3). Pitcher et al. were able to reproduce findings, which were already examined by fMRI. By the use of rTMS, they localized the right-sided inferior occipital gyrus (occipital face area) as an early stage of the face-processing stream (Gauthier et al. 2000; Pitcher et al. 2007). These results were confirmed by a subsequent study of the same group. Moreover, they showed that the application of rTMS over the right-sided lateral occipital area impairs the discrimination of objects but not of faces. The same results were found when stimulating the right-sided extrastriate body area (Pitcher et al. 2009). In 2008, the group of Pitcher already described the involvement of the right somatosensory area in the course of face processing as examined by rTMS. Similarly, this gives evidence for the contribution of nonvisual

areas to expression processing (Pitcher et al. 2008). The latter also replicates the results of another rTMS study (Pourtois et al. 2004). Furthermore, nrTMS could prove the contribution of the occipital face area as well as the superior temporal sulcus in the judging of gender and trustworthiness of faces (Dzhelyova et al. 2011). Another well-experienced group in nrTMS showed the involvement of the right-sided occipital face area in the integrative processing of facial identity and expression (Kadosh et al. 2011).

Maurer et al. performed a study for the mapping of face processing by the use of nrTMS. Healthy subjects were asked to name 80 portraits of popular persons during the stimulation of predefined cortical sites of the whole hemisphere (Maurer et al. 2017). They differentiated between language errors and errors regarding the wrong identification of persons. Despite the results did not show statistically significant differences, the locations were in good accordance with current literature (Barton 2014; Yang et al. 2014; Gomez et al. 2015). Moreover, they found a more important role of the right-sided frontal lobe in face processing than previously expected. The latter also correlates with earlier results of rTMS and PET studies (Campanella et al. 2001; Renzi et al. 2013). However, as Maurer et al. also conclude, particularly the mapping of face processing reveals the limitations of nrTMS: parts of the functional network of face processing such as the limbic system are not reachable for TMS since they are located subcortically (Leonard et al. 1985; Gothard et al. 2007).

By the experiences of multiple studies, the application of emotion and identity recognition tasks based on pictures of standardized datasets seems to be most effective (Table 11.3). Since the course of face processing is more complex, DT has to be longer, for example, 700 ms. Again, when concluding previous works, repetitive pulses with a frequency of 5–10 Hz and simultaneous pulse and stimulus onset (PTI = 0 ms) are recommended for a reliable inhibition of face processing.

11.3.1 Categorizing

Neuropsychological literature discusses different theories to explain the basis of the human ability to categorize (Caramazza and Shelton 1998; Caramazza and Mahon 2003; Humphreys and Forde 2001; Martin et al. 1996; Warrington and Shallice 1984). Furthermore, it has been discussed that natural/living and artificial/nonliving domains of the underlying semantic knowledge are represented in separate subsystems and anatomical locations (Paz-Caballero et al. 2006; Devlin et al. 1998; Martin et al. 1996; Perani et al. 1995). The subsystems of these theories have already been visualized by fMRI, PET, and event-related potentials (ERP) as measured by EEG or MEG (Chao et al. 1999; Moore and Price 1999; Grafton et al. 1997; Damasio et al. 1996; Martin et al. 1996; Perani et al. 1995; Paz-Caballero et al. 2006; Kiefer 2001, 2005; Sim and Kiefer 2005; Dehaene 1995).

The latter technique has also been used in combination with TMS in order to show the functional representation of living and nonliving domains across both hemispheres. In 2009, Fuggetta et al. were able to impair the categorization of artificial/nonliving items by disrupting Wernicke's area with rTMS and thereby

Fig. 11.3 Categorization task. The figure shows examples of living and nonliving objects. The task can be used for the mapping of the cortical localization of categorizing

supported the theory that semantic knowledge is associated with different conceptual domains based on a network of segregated systems of functionally connected cortical areas (Fuggetta et al. 2009). Passeri et al. also applied rTMS to Wernicke's area and its right-sided homologue in order to investigate the semantic categorization process and the contribution of both hemispheres. They used a verbal category membership task consisting of words referring to typical and atypical exemplars and could show the involvement of both hemispheres in the categorization process of typical exemplars while the right-sided hemisphere was involved in the categorization of atypical exemplars (Passeri et al. 2015). Thereby, they confirmed the Jung-Beeman theory, which describes a coarser semantic processing in the right-sided in comparison with the left-sided hemisphere (Jung-Beeman 2005). Another group investigated the cortical localizations of categorization by nrTMS. They used a task consisting of 80 living and nonliving objects and stimulated 52 predefined cortical sites over both hemispheres (Fig. 11.3). In Maurer's study, the highest ER on the left hemisphere was located within the MFG and the SMG. For the right hemisphere, the highest ER was found within the parietal lobe, too. Taken together they showed the feasibility of successfully interfering the categorization process by nrTMS as well as the accordance of the results with current literature (Maurer et al. in preparation).

As Table 11.4 shows, several tasks have been used to map the cortical localization of categorizing in the past. Since the process of categorization is complex, it is difficult to give a recommendation for the most effective mapping parameters. However, most researchers use repetitive pulses with a frequency of 5–10 Hz and a simultaneous pulse and stimulus onset (PTI = 0 ms).

11.3.2 Future Aspects

The abovementioned studies and approaches for the mapping of brain functions apart from motor and language function are equally important for neurosurgery and basic neuroscientific research. Particularly nrTMS confirmed the feasibility of mapping further brain functions like arithmetic processing and visuospatial attention in

healthy subjects and similarly represents an accurate technique for basic researchers. Thereby, its application in patients for preoperative mapping seems justified and enables neurosurgeons to transfer preoperative nrTMS data to the operating room. This might shorten the intraoperative DES mapping procedure and decreases the patient's burden. Additionally, it allows the evaluation of different tasks preoperatively in order to choose the most effective task for the intraoperative procedure.

However, as resection probability maps and clinical experience have shown, the preservation of subcortical fibers is equally important when aiming for functional integrity (De Witt Hamer et al. 2013; De Benedictis and Duffau 2011; Duffau 2014). Thus, the approach of nrTMS-based DTI-FT seems also reasonable to be combined with these data. Thereby, the use of nrTMS-based DTI-FT enables the visualization of subcortical networks, which are associated with further cortical functions apart from language. By transferring the DTI-FT data to neuronavigation systems, they can also be used for preoperative planning as well as intraoperative guidance (Fig. 11.4).

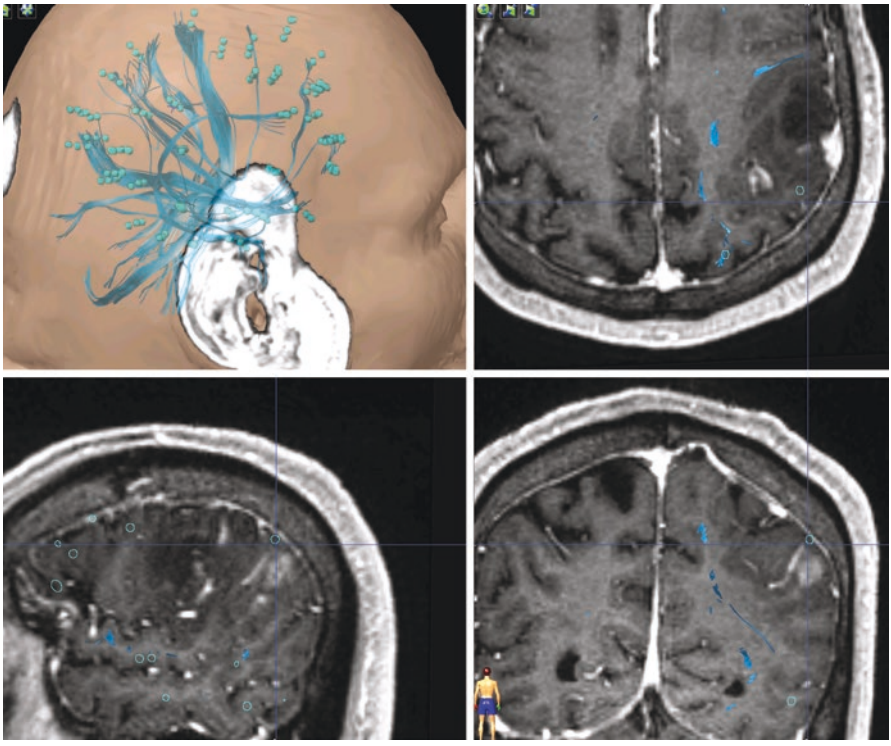

Fig. 11.4 nrTMS-based DTI-FT. The figure shows the results of the preoperative mapping of arithmetic processing by nrTMS as transferred to the intraoperative neuronavigation system (iPlan Net Cranial 3.0.1, Brainlab AG, Munich, Germany). Arithmetic processing-positive cortical sites in terms of nrTMS are used as ROI for nrTMS-DTI-FT. The figure shows the preoperative neuronavigation of a 76-year-old male with a glioblastoma within the right parietal lobe

However, the technique still has to be further refined. Up to now, nrTMS studies investigating neuropsychological brain functions apart from language have often been performed using a stimulation frequency of 5–10 Hz (Tables 11.1–11.4) (Giglhuber et al. 2016; Maurer et al. 2016). These parameters have been chosen due to experiences from language mapping. Still, earlier studies have shown that the use of different stimulation frequencies affects the distribution of language-positive sites, for example Hauck et al. (2015a). Likewise, choosing the proper task is also crucial for obtaining relevant results when mapping higher cortical functions, such as language (Hauck et al. 2015b). These two issues might also be appreciable for the mapping of neuropsychological brain functions. Especially the choice of tasks seems to be crucial (Coello et al. 2013). As a further step, the reliability and clinical usefulness of mapping these functions must be confirmed in neurosurgical patients.

As described, the mapping of further cortical functions by nrTMS offers a tremendous preoperative mapping potential for neurosurgeons. However, it is clinically not reasonable to map each possible brain function in each patient. The choice of tasks for the preoperative as well as the intraoperative mapping is also a decision, which functions need to be preserved for each individual patient in the current oncological situation. Thus, it must be tailored to each patient's personal situation, occupation, and the location and type of the pathology. If done under these premises, nrTMS might contribute to a useful neurocognitive assessment (Duffau 2013).

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nTMS in Pediatrics: Special Issues and Solutions

12

Harper Lee Kaye and Alexander Rotenberg

12.1 Introduction

A safe and well-tolerated noninvasive method for reliable motor and language functional cortical mapping in children is an important unmet need that may be addressed by nTMS. Current presurgical planning techniques, such as the Wada test and fMRI, are often difficult to obtain in children. Yet, many children require surgical resection of pathologic tissue in the region of eloquent neocortex. The nTMS technique thus offers a practical option for pediatric neurology and neurosurgery centers, particularly those focused on management of children with brain tumors and/or intractable epilepsy.

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12.2 Epidemiology

Neocortical resective surgery is relatively common in children and drives the need for noninvasive presurgical functional mapping in this specialized population. Focal pharmacoresistant epilepsy, where seizures arise from the cerebral convexity rather than from the temporal lobes, for instance, is more prevalent in children than in adults (Clusmann et al. 2004; Berg et al. 2012; Griessenauer et al. 2015). This is attributed in part to a pediatric predominance of syndromes that are associated with intractable seizures, such as malformations of cortical development and tuberous sclerosis, which are more likely to manifest symptomatically and require surgical resection of a seizure focus in early life (Dorfmüller et al. 2014; Weiner et al. 2004). As well, a range of neuroclastic syndromes such as sequelae of perinatal stroke, Sturge-Weber syndrome, and Rasmussen's encephalitis are more common in the pediatric population or are identified in early life due to their propensity to trigger seizures (Duchowny 1989; Saneto 2005).

Supratentorial brain tumors in children, while less common than in adults, also account for an appreciable fraction of pediatric neocortical resective surgeries and cases of intractable seizures (Clusmann et al. 2004; Macedoni-Lukšič et al. 2003; Giulioni et al. 2009). While only 1% of childhood epilepsy is related to brain neoplasm, a much larger fraction (~50%) of children with supratentorial tumors have seizures (Holmes 1996).

12.3 Conventional Preoperative Methods for Localization of Function: The Wada Test and FMRI

Young pediatric patients are often unable to comply with conventional mapping protocols—particularly the relatively invasive clinical gold standards and the noninvasive functional neuroimaging techniques, which are better suited for the adult population (Bahn et al. 1997; Perry et al. 2011). Dr. Wada's intracarotid amobarbital procedure (IAP) is commonly used in presurgical evaluation for both adult and adolescent patients, as a way to lateralize language and memory dominance prior to a resective surgery (Spencer et al. 2000; Loring et al. 1992, 1994; Sperling et al. 1994). Yet the presurgical IAP is used less frequently in pediatric neurosurgical evaluation due to concerns for radiation exposure and potential risk for moderate (0.3%, allergic reaction to contrast; 0.1%, bleeding from the catheter insertion site; 0.1%, infection) to severe (7.2%, encephalopathy; 1.2%, seizure; 0.6%, stroke; 0.6%, transient ischemic attack; 0.6%, hemorrhage at catheter insertion site; 0.4%, carotid artery dissections) complications (Loddenkemper et al. 2008). Superimposed on the health risks of the IAP are also problems with behavioral management and with adaptation for age-appropriate test items such that simplified testing batteries for children, when coupled with a reduced amobarbital dose, at times compromise the IAP results (Saneto 2005). Thus, the IAP establishes language dominance for fewer than two thirds of preadolescent children (Bahn et al. 1997).

Clinical fMRI for language mapping may yield lateralization results similar to that of the gold standards, such as the Wada test or mapping analogous to cortical DES (Kwan et al. 2010; Beers and Federico 2012; Garrett et al. 2012). Conventional expressive language mapping tasks such as antonym generation or receptive/whole language tasks such as auditory response naming show robust activation of the frontal and temporal lobe in adults and older children (Szaflarski et al. 2017). Yet, such strongly implicated regions of activation require full cooperation inside the MRI scanner, which in children promotes a higher likelihood of poor task compliance or confounding by excess patient motion (Branco et al. 2006; Price et al. 2006).

Motor mapping by fMRI is also compromised by limited cooperation of pediatric patients. For instance, performance of active movement tasks without physical constraint cannot correct for the pace at which a movement is initiated, the force of the movement, and movement length or duration (Price et al. 2006).

Sedation is at times used to counterbalance the effects of young age and behavior dysregulation during fMRI. While sedated, the operator will manually manipulate a given joint, and the activation pattern detected during such passive movement is used to map motor function. Similarly, passive language tasks in sedated children are used as they do not require overt patient participation and can be acquired in a short period of time (~7 min) (Hertz-Pannier et al. 1997; Souweidane et al. 1999). However, the interpretation of resultant passive/sedated motor and language maps, both of which have appreciable volitional behavioral components, is problematic in the young patient age group.

12.4 Special Considerations for NTMS in Children

Developmental considerations and cognitive limitations of pediatric patients are factors pertinent to the success of nTMS mapping. Head circumference, skull thickness, degree of myelination, limb length, and other such factors should be taken into account during nTMS in pediatrics. Yet, more pedestrian factors such as cooperation, subject body size relative to the chair in the nTMS lab, or limb size relative to EMG electrodes govern the practical application of nTMS in this population. Fortunately, these are surmountable obstacles.

A common problem is the need to adapt adult-based nTMS accessories to children. The mechanics of the chairs that are available are adequate for the intended use in larger patients, but are suboptimal when working with a small child. For this reason, supportive cushions, which are tightly fitted to the chair used during the session, must be fitted to remain in place, as to prevent the child from sliding or moving during stimulation, and are a necessary tool to keep readily available. In very young patients (<3 years old), a family member may sit in the chair to hold the child in his or her lap.

A similar technical difficulty encountered in pediatric nTMS is difficulty with securing the surface EMG electrodes, in a way that circumvents the child's ability to remove the electrodes during the session. Thus, a sufficient amount of medical tape can be used such that the risk of electrode removal is minimized. In locations

where hairy skin is present, removal of this tape can be painful for children, leading to transient skin erythema.

In some nTMS models, the child must wear a head reflector, which allows tracking by stereo camera. This reflector is secured around the circumference of the head with an elastic band. Once nTMS registration is performed, this head tracker must remain in location on the forehead for the duration of the stimulation to ensure neuronavigational accuracy. Due to the tension of the elastic band and the pressure of the plastic on the forehead, children frequently complain of headache during the nTMS session. To mitigate the discomfort of the band and the experience of headache, a wax pen may be used to mark the precise position of the reflectors such that these can be removed for some time if the patient expresses discomfort and then replaced without having to re-register the relative positions of scalp landmarks. This marking helps to ensure that any movement of the reflectors during the session is visible to the operator and can be corrected for.

In situations where nTMS is hindered by behavioral dysregulation, creativity on the team's behalf is necessary. Often, a member of the stimulation team or a patient's family member is asked to hold a tablet or cellular phone in front of the child, displaying a favorite video, as a way to draw attention away from the stimulation or to encourage a child to face the stereo camera for the duration of the nTMS session. In such cases, or when patients have difficulty completing a session, it is often helpful to break a single mapping session into multiple session visits. This requires a small degree of additional planning on behalf of the family and calls for additional scheduling on behalf of the hospital administrators, but the benefits of obtaining full motor and/or language maps for presurgical patients far outweigh any inconvenience.

12.5 Stimulation Parameters

12.5.1 Age and Motor Threshold

The age limit for activating the motor cortex by TMS is potentially lowest in the neonate, as demonstrated by Eyre et al. in 2001 (Eyre et al. 2001; Lin et al. 2002; Koh and Eyre 1988). However, the biology of the developing brain may impose practical limits on TMS in general, and on nTMS in particular. For instance, age is reliably negatively correlated with rMT (Fig. 12.1), which in children is operationally defined as in adults (for instance, the minimum stimulator output, also quantified in electrical field strength, necessary to elicit a response from an intrinsic hand muscle, contralateral to the stimulated hemisphere, of 50 μV, on ≥50% of trials). In the authors' experience, patients younger than 4 years of age will very likely require stimulation to be performed at 100% stimulator output in order to reliably elicit MEPs from the target muscles—particularly when mapping proximal upper extremity muscles and the lower extremities.

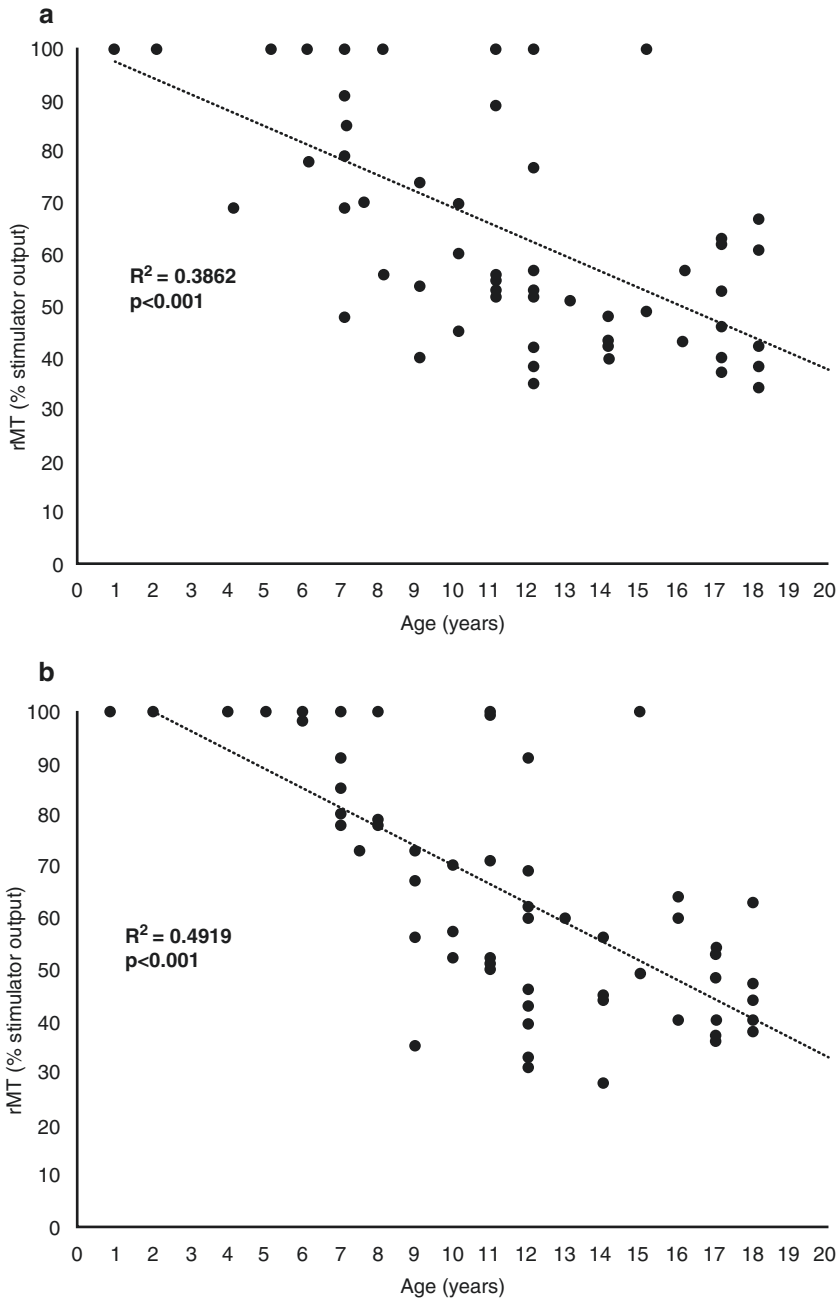

Fig. 12.1 Correlation between rMT and age. Patient data (Kaye et al. 2017) from children with epilepsy, where age (*x*-axis; in years) is negatively correlated with rMT (**b**) right hemisphere (% stimulator output) (**a**) left hemisphere (% stimulator output) (**d**) right hemisphere (V/m) and (**c**) left hemisphere (V/m) for the right and left intrinsic hand muscles. The range of field strength is broad: 117.35 ± 40.80 V/m (mean ± SD). Patients younger than 4 years of age require stimulation to be performed at 100% stimulator output

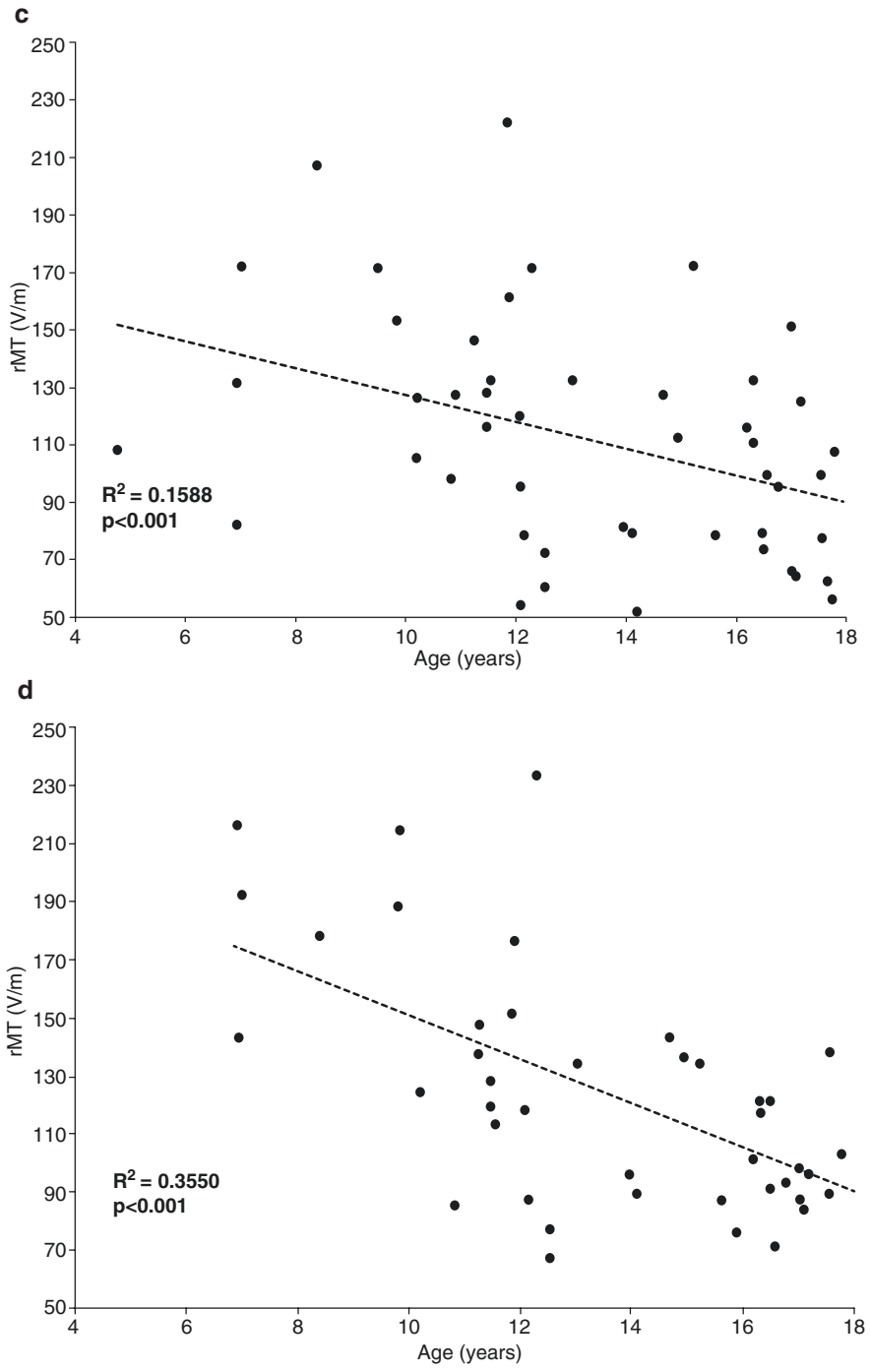

Fig 12.1 (continued)

12.5.2 nrTMS for Language Mapping

The nrTMS language mapping protocols require specialized considerations in children. In the authors' clinical program, the NexSpeech® software (Nexstim Plc., Helsinki, Finland) is used for language mapping. The common task used in children is an object-naming task, where objects are presented visually at baseline for time-limited blocks and then are represented coupled with repetitive stimulation, typically 5 Hz, in 1 s trains. The stimulus intensity for language mapping in children is calibrated from a starting point of 120% rMT to the maximal stimulator output tolerated, which is often lower than rMT. The outcome measures in this task are word generation and accuracy of object naming. However, appreciable flexibility in these settings is needed to accommodate the range of development across the pediatric population. Most often, a long latency in verbal response relative to the timing of the visual stimulus in the object-naming task requires either an increase of the interval between successive images or a prolongation of the stimulation train. The relatively slow verbal response of pediatric patients to presented visual stimuli also modifies the post hoc analysis such that delays in response are difficult to interpret and in the authors' practice only speech arrest or paraphasic errors are scored to generate the pediatric language map in young children.

Another practical limitation in pediatric language mapping is the relatively high rMT in children, which obligates stimulation intensities beyond the threshold for tolerability in many patients. With smaller head sizes as compared to adults, rTMS to inferior frontal regions is likely to cause peripheral activation of the facial muscles and at appreciable intensities causes discomfort and language arrest that is ambiguous in origin.

12.6 Special Population: Children with Epilepsy

As noted above, a high number of children who will benefit from resective neurosurgery and antecedent nTMS are patients with intractable epilepsy, yet the majority of patients with intractable seizures are on one or more antiepileptic drugs at the time of nTMS, which likely translates to altered rMT. For instance, voltage-gated sodium channel blockers such as oxcarbazepine, lamotrigine, and lacosamide are common in the authors' patient population and likely contribute to an increase in the rMT in our patients (Paulus et al. 2008). Notably, while the effects of many common central nervous system medications on TMS metrics have been described, the interaction of these agents with developmentally regulated physiologies that alter such outcome measures remains unknown.

12.7 NTMS Safety in Children

The use of TMS, particularly rTMS as applied in navigated language mapping, may trigger seizures in some subjects. This may be a more relevant concern for pediatric patients, who may have lower seizure thresholds than adults (Pohlmann-Eden et al.

2006). Encouragingly, very few instances of seizure have been recorded in children undergoing nTMS. In the authors' population of children with epilepsy, a population that is by definition seizure-prone, only 2–3% (4 of >150 patients) have had a seizure during motor mapping with nTMS, and of ~2% (1 of >40) patients have had a seizure during language mapping with nrTMS. However, all observed seizures were the patients' habitual seizures. Whether these were causally induced by nTMS/nrTMS or coincidentally occurring during the mapping sessions is not clear. Notably, no instance of atypical seizure or status epilepticus has been recorded in any child undergoing nTMS.

12.8 NTMS: FMRI Discrepancy

Chapter 2 outlines the differences of other noninvasive techniques, such as MEG and fMRI, as compared to nTMS in detail.

In the authors' experience, which is corroborated by data in published reports, motor maps resultant from fMRI protocols and the motor maps created by nTMS motor mapping can, at times, yield discrepant results. For instance, Zostor and colleagues used both fMRI and nTMS preoperatively to evaluate the functional organization of the sensorimotor system in children being evaluated for hemispherectomy. While nTMS of the lesioned hemisphere elicited no hand MEPs, and nTMS of the contralesional hemisphere elicited bilateral hand MEPs, fMRI detected functional signal in the lesional, epileptic hemisphere during a motor task restricted to the affected (contralateral to the cortical lesion) hand. Thus, fMRI analysis in this cohort indicated activation in the epileptic hemisphere, while nTMS indicated absent corticospinal connectivity in the lesional hemisphere. Notably, in all patients in this small series, postsurgical (post-hemispherectomy) motor function was preserved for the hand corresponding to lesional cortical activation by fMRI. Thus, in some instances, an absent corticospinal signal obtained by nTMS is an adequate predictor of a subsequent absence of motor deficit, even if the lesional hemisphere contains an fMRI signal for a motor task.

12.9 Conclusion

Neocortical resective surgery is unique in the challenges of operating in the proximity of eloquent cortex. In some diseases, such as focal intractable epilepsy, an appreciable fraction of neocortical resections are destined to be in the pediatric population. In such instances, localization of the areas responsible for motor and language processes is critical to the planning and execution of the neurosurgical procedure. Using nTMS/nrTMS for motor and language mapping is becoming increasingly valued in presurgical planning in adult neurology and neurosurgery and is also emerging as a valuable tool in pediatric presurgical planning as well. The nTMS/nrTMS technique has demonstrable utility for obtaining the information needed for localization of motor and language function in the pediatric population, with

minimal associated health risks to the child and very little difficulty on behalf of the operator. In contrast to intraoperative or similar invasive cortical stimulation, the noninvasive and safe nature of nTMS enables its use in both affected and the unaffected hemispheres. As the authors' patient population is primarily children with pharmacoresistant epilepsy, nTMS/nrTMS in our institution enables collection of critical information about cortical reorganization, which is not uncommon in children with early-onset epilepsy in the developing brain (Kaye et al. 2016, 2017). Conservation of function in the dysplastic cortex, atypical motor and/or language representation, and relocation outside the affected area are readily seen with nTMS/nrTMS mapping in children with early life brain disorders. Knowledge of such reorganization through mapping, for the neurosurgeon intraoperatively and for successful postsurgical outcome, argue for expanded use of nTMS/nrTMS in pediatric resective surgery planning.

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Part V

Therapeutic Applications in Neurosurgery

Navigated rTMS for the Treatment of Pain

13

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13.1 Introduction

Neuropathic pain originates from a lesion or disease of the central or peripheral somatosensory system (Treede et al. 2008) and affects up to 8% of the general population (Bouhassira et al. 2008). Pharmacological interventions have limited efficacy in this domain and satisfactorily relieve neuropathic pain in only 30–40% of patients (Attal et al. 2006). Developed in the early 1990s (Tsubokawa et al. 1991a, b), epidural stimulation of M1 using surgically implanted electrodes was shown to produce long-term analgesia in about half of the patients with chronic neuropathic pain resistant to medication (review in: Cruccu et al. 2007, 2016; Fontaine et al. 2009; Nguyen et al. 2009). Since the end of the 1990s (Lefaucheur et al. 1998, 2001a, b), noninvasive stimulation of M1 using rTMS has been successfully applied in the same clinical context (review in: Lefaucheur 2006, 2008a, 2016; Leung et al. 2009).

13.2 Clinical Evidence

A group of international experts found level A evidence for the efficacy of rTMS on neuropathic pain when applied at HF, i.e., 5–20 Hz, over M1 contralateral to the painful side (Lefaucheur et al. 2014). Stimulation frequency was found to be one of the most crucial rTMS parameters to ensure analgesic effects. In patients with chronic neuropathic pain, analgesia can be produced by the administration of HF rTMS (5–20 Hz) over M1, but not LF rTMS (0.5–1 Hz) (Lefaucheur et al. 2001a; André-Obadia et al. 2006; Saitoh et al. 2007). Moreover, one study demonstrated

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that 10 Hz rTMS is more efficacious than 5 Hz rTMS (Saitoh et al. 2007), supporting the preferential use of 10 or 20 Hz frequency in this domain.

When considering sham-controlled studies (with a crossover or parallel-arm design), including at least ten patients receiving active stimulation for at least 5 consecutive days, various studies have reported the beneficial effect of HF rTMS over M1 on neuropathic pain, even at midterm (from 1 to 6 weeks beyond the time of stimulation) (Khedr et al. 2005; Kang et al. 2009; Ahmed et al. 2011; Fricová et al. 2013; Hosomi et al. 2013; Yılmaz et al. 2014; Khedr et al. 2015). These analgesic effects were obtained whether the anatomical origin of neuropathic pain was central or peripheral. A figure-of-eight coil was used in all cases, delivering a relatively focal electric field within the motor cortex. The use of circular and double cone coils delivering a larger electric field was found to be ineffective (Rollnik et al. 2002). Other types of coils, producing even more widespread and deeper cortical stimulation, such as the H-coil, may have some value for producing analgesia (Onesti et al. 2013), but this remains to be confirmed.

13.3 General Methodology

An important methodological question is posed by the precision of the placement of the stimulating coil due to the use of a relatively focal stimulation. From an anatomical perspective, two different issues must be addressed, whether one considers the rostrocaudal or the mediolateral axis. Firstly, regarding the rostrocaudal axis, the question relates to the respective location of M1 and the cortical stimulation site capable of producing optimal analgesic effects, with respect to the precentral gyrus and the central sulcus. Secondly, regarding the mediolateral axis, it concerns whether the effects of motor cortex stimulation are somatotopic or not.

Concerning the rostrocaudal axis, it is known that M1 occupies the anterior wall of the central sulcus and only a limited part of the exposed surface of the precentral gyrus (Geyer et al. 2000; Rademacher et al. 2001). This fact would justify the stimulation of the posterior bank of the precentral gyrus and the use of a navigation system for this purpose. Indeed, the other ("standard") method that can be used to target the stimulation is based on the determination of the motor hotspot. The motor hotspot is, by definition, the scalp position where a single-pulse TMS generates the largest MEP in a given muscle. However, it has been demonstrated that, in at least half of the subjects, the motor hotspot is located in the precentral gyrus, close to the precentral sulcus, and thus very far from the central sulcus (Ahdab et al. 2016). This anterior shift was reported by several groups (Denslow et al. 2005; Teitti et al. 2008; Ahdab et al. 2010; Diekhoff et al. 2011; Julkunen et al. 2011) and can be explained by two factors: (1) the presence of pyramidal neurons at the origin of CST within the cortical premotor areas (He et al. 1993, 1995) and (2) the indirect activation of CST in M1 via the dense projections that connect the PMC and M1 (Ghosh and Porter 1988; Shimazu et al. 2004). Whatever the underlying reason, it is certain that the location of the hotspot could not be considered a reliable marker to precisely locate M1 at the level of the central sulcus. Moreover, under pathological conditions, this anatomical

relationship becomes more ambiguous. This is due to the cortical plasticity induced by the disease process, as it can be evidenced, for example, by preoperative cortical motor mapping (Lefaucheur and Picht 2016). Therefore, it is essential to use a navigation system if the objective is to precisely target the central sulcus.

13.4 The Role of Neuronavigation

The justification for using anatomical data (anterior lip of the central sulcus) rather than functional ones (motor hotspot location) to target the stimulation of the motor cortex stems from the fact that the analgesic effects are not directly related to the activation of pyramidal neurons or the cortical motor output. Modeling studies have shown that the analgesic effects are related to the activation of axons, which run in the superficial cortical layers at the top of the crown of the precentral gyrus, tangential to the cortical surface and close to the central sulcus (Holsheimer et al. 2007a, b; Manola et al. 2007; Nguyen et al. 2011). Hence, to produce analgesic effects by preferentially stimulating those fibers with a figure-of-eight coil, the handle of the coil must be oriented in an anteroposterior direction, parallel to the interhemispheric fissure (André-Obadia et al. 2008; Lefaucheur et al. 2010). Maintaining this orientation stable during stimulation sessions constitutes an additional reason for using a navigation system. To conclude about the "rostrocaudal" issue, there are several arguments in favor of targeting the posterior part of the precentral gyrus (anterior lip of the central sulcus). This can only be precisely achieved by means of nTMS, because MEP-based targeting is reliable in terms of motor output function rather than cortical anatomy. However, the superiority of such a targeting strategy remains to be demonstrated formally on clinical grounds.

In the mediolateral axis, the optimal location of coil placement to relieve pain remains speculative. The main question is whether the analgesic effects of stimulation are somatotopic (i.e., related to a precise anatomical cortical targeting according to pain location) or not. Furthermore, even if the analgesic effects of stimulation are somatotopic, it remains to be determined whether they are homotopic (i.e., depending on the actual targeting of the precise cortical representation of the painful region) or not. In this context, it has been shown, for example, that patients with facial pain might be improved by stimulating the hand rather than the face area, whereas patients with hand pain might be improved by the stimulation of the face rather than the hand area (Lefaucheur et al. 2006). Although this result has not been reproduced in all studies, particularly following nrTMS (Ayache et al. 2016), this poses a problem as to the necessity and interest of stimulating specifically the cortical region that corresponds to the painful area. Moreover, even if we have some convictions and personal experience about the somatotopic analgesic effects of invasive or noninvasive motor cortex stimulation, this cannot be considered a general rule. There is indeed evidence that these analgesic effects are not always somatotopic. It should be mentioned in particular that a focal stimulation of the motor cortex can be beneficial on diffuse pain syndromes, for example, in the case of fibromyalgia (Passard et al. 2007; Mhalla et al. 2011; Boyer et al. 2014).

In most rTMS studies based on motor hotspot targeting, analgesic effects have been obtained by targeting the cortical representation of the hand contralaterally to the painful side, whatever the location of pain was (Lefaucheur et al. 2004b, 2008b; Khedr et al. 2005; André-Obadia et al. 2006, 2011; Kang et al. 2009; Matsumura et al. 2013). This was also the case for one nrTMS study (Lefaucheur et al. 2012). However, if the outcome of motor cortex rTMS is influenced by somatotopy, at least in some patients, the anatomy of the cortical motor representations should be taken into consideration. The segment of the central sulcus facing the SFG (=F1) corresponds to lower limb motor representation, the MFG (=F2) to the upper limbs, and the IFG (=F3) to the face (Fig. 13.1) (Penfield and Boldrey 1937; Nguyen et al. 1999; Ahdab et al. 2014). Very few studies have used image-guided navigation systems to target motor cortex rTMS for pain therapy (Hirayama et al. 2006; Hodaj et al. 2015; Ayache et al. 2016). In one of these studies (Ayache et al. 2016), the analgesic effects produced in patients with chronic neuropathic pain by nrTMS targeted on the anatomical representation of the pain area on the motor cortex were compared to those produced by (nonnavigated) rTMS targeted on the hand motor hotspot, irrespective of the pain location. Short-lasting analgesia was produced in patients with unilateral upper or lower limb pain by both procedures, but the effects were more prolonged following nrTMS of the painful limb's cortical motor representation. However, it remains to be demonstrated that nrTMS leads to a better

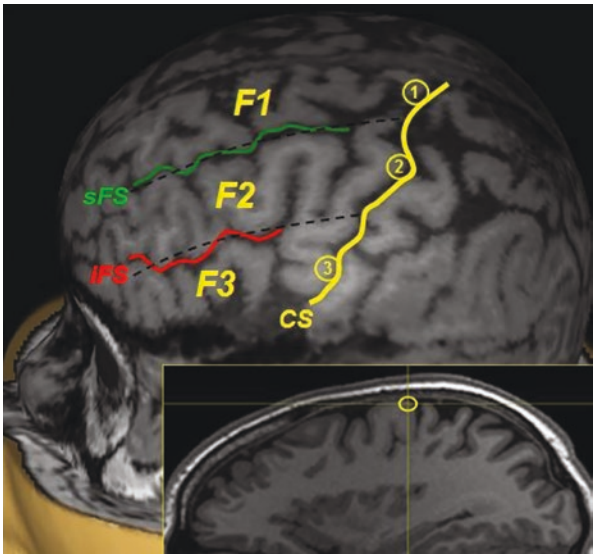

Fig. 13.1 Motor cortex targets for nrTMS pain therapy. Motor cortex targets for nrTMS pain therapy, anatomically located on the anterior bank of the central sulcus. On the mediolateral axis: (*1*) lower limb target facing F1 (=SFG), above the level of the superior frontal sulcus (sFS); (*2*) upper limb target facing F2 (=MFG), above the level of the inferior frontal sulcus (iFS); (*3*) face target facing F3 (=IFG), below the level of the iFS. On the rostrocaudal axis (sagittal view, inferior part of the figure): the target is located at the top of the anterior wall of the central sulcus, i.e., at the posterior border of the precentral gyrus (adapted from Ayache et al. 2016)

outcome when it targets the cortical motor representation of the painful region rather than an adjacent cortical motor region or even the cortical hand motor representation (hand knob) regardless of the location of pain.

13.5 Potential Mechanisms

The mechanisms underlying the analgesic effects of rTMS are not well known, but they probably involve a modulation of various pain control pathways. Indeed, since rTMS-induced currents activate axons more easily than cell bodies (Nowak and Bullier 1998a, b), the mechanisms of action of cortical stimulation must be modeled in terms of neural circuit rather than local brain activity changes. Therefore, in the future, integration of tractography data provided by DTI could be of particular interest for the treatment of pain by nrTMS. In this regard, it should be mentioned that two studies have shown, using tractography data, that the integrity of the thalamocortical tract predicted the beneficial effects of HF rTMS of M1 in patients with central poststroke pain (Goto et al. 2008; Ohn et al. 2012), supporting the hypothesis of an implication of the antidromic modulation of thalamocortical pathways in the analgesic effect of motor cortex stimulation.

It should be added that the interest of navigation could be even greater in the case where the target is located outside M1, e.g., in the DLPFC. Actually, few rTMS studies have investigated the value of stimulating the left DLPFC at HF (10 Hz) or the right DLPFC at LF (1 Hz) to produce analgesic effects, in the light of what was demonstrated for the antidepressant effects of rTMS. Beneficial results of both types of prefrontal stimulation have been reported (1) in neuropathic pain (Borckardt et al. 2009; Sampson et al. 2011; Nardone et al. 2017), although it remains controversial (de Oliveira et al. 2014), and (2) in nonneuropathic pain syndromes (Umezaki et al. 2016), including diffuse pain syndromes, such as fibromyalgia (Sampson et al. 2006; Short et al. 2011; Lee et al. 2012). However, the DLPFC target definition appears rather imprecise, especially because of the large extent of this cortical area (Nauczyciel et al. 2011; Mylius et al. 2013; Pommier et al. 2017). Thus, it remains to be determined whether prefrontal stimulation can really benefit from a navigation-based anatomical targeting compared to a more conventional motor hotspot-based functional targeting.

The benefit of using a navigation system is also based on the repeated or long-term use of rTMS for pain therapy. Indeed, the repetition of daily rTMS sessions with at least 1000 pulses per session for 1 or 2 weeks (5 or 10 sessions) is able to produce cumulative effects and to reduce pain scores by 20–45% for at least 2 weeks beyond the time of stimulation (Khedr et al. 2005, 2015; Ahmed et al. 2011; Fricová et al. 2013; Hosomi et al. 2013). The overall rate of responders can be estimated between 35% and 60% (Lefaucheur et al. 2014). However, to induce long-lasting analgesic effects compatible with a therapeutic use of rTMS in clinical practice, repeated sessions performed at regular intervals (maintenance treatment) are required. Under these conditions, beneficial effects of HF rTMS of M1, lasting more than 6 months, have been reported in patients with fibromyalgia (Mhalla et al. 2011),

refractory facial pain (Hodaj et al. 2015), or central neuropathic pain (Pommier et al. 2016). Performing repeated rTMS sessions over long periods can be facilitated by the use of a navigation system that stores the individual coordinates of the optimal stimulation target for a given patient (Lefaucheur 2010). Obviously, navigation systems can improve, in real time, the reproducibility (repeatability) of an accurate coil placement during and between sessions, compared to a targeting based on cranial landmarks plotted on a head cap.

13.6 nrTMS for Preoperative Testing

A last remark concerns the practice of nrTMS as a preoperative test for invasive chronic epidural motor cortex stimulation by means of surgically implanted electrodes. It has been demonstrated that the clinical response to HF rTMS of M1 correlated with a favorable outcome of the surgical procedure (André-Obadia et al. 2006; Hosomi et al. 2008; Lefaucheur et al. 2004a, 2011). The absence of response to preoperative nrTMS tests was even correlated with a poor result of chronic motor cortex stimulation at the long term (André-Obadia et al. 2014). Moreover, rTMS and epidural motor cortex stimulation likely share common mechanisms of action (Lefaucheur et al. 2010). Also, it could be envisaged to use the coordinates of the target validated by the preoperative nrTMS tests to guide the placement of the epidural electrodes during the surgical procedure. Unfortunately, data are lacking in this respect, as preoperative studies published to date were performed using non-navigated rTMS techniques.

13.7 Conclusion

It remains to be confirmed that the analgesic efficacy of motor cortex rTMS depends on a precise anatomical targeting, which could benefit from a system of image-guided navigation using morphological or functional brain imaging. As of today, the clinical relevance of a navigated approach of rTMS pain therapy is not a certainty (Klein et al. 2015), even though navigation clearly facilitates everyday practice, particularly with regard to the reproducibility of the procedure. Concerning the optimization of motor cortex rTMS targeting for pain therapy, the main questions to be answered are as follows: (1) Is anatomical targeting of the anterior bank of the central sulcus better than functional targeting of the motor hotspot, whose location varies between subjects? (2) Is anatomical or functional targeting of the painful region better than that of the hand, regardless of the location of pain? In the absence of a formal response to these two questions, it seems preferable to evaluate in each individual patient the respective analgesic efficacy of various cortical motor targets, e.g., the anatomical representation of the hand (hand knob), the motor hotspot of the hand, and the anatomical representation or motor hotspot of the painful region if the latter is not located at the hand. An image-guided navigated procedure is surely a relevant strategy to achieve a more personalized approach tailored to each patient regarding rTMS pain therapy in clinical practice.

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Treatment of Paresis

14

Jari Karhu and Petro Julkunen

14.1 Background of Current Paresis Treatment Approaches

Most of the discussion related to treatment and rehabilitation of paresis in this chapter is rooted in stroke rehabilitation conventions and practices; stroke is by far the most prevalent reason leading to paresis and, in about half of patients, permanent impairment of motor function. Still, there is ample evidence that rehabilitation therapy focusing on repetitive and skillful task practice (task-oriented therapy) results in long-term functional recovery. Both animal models (Kleim and Jones 2008) and human clinical trials (Liepert et al. 2000; Wolf 2006) support a use-dependent relationship between task-oriented therapy, neuroplasticity, and functional performance. However, in clinical rehabilitation, functional recovery of arm and hand function is limited to about 50% of patients with stroke, and full recovery is achieved in less than 20% (Kwakkel et al. 2003). Interestingly, there is no definite evidence that a certain standardized therapy protocol or a certain threshold of therapy intensity (e.g., Lang et al. 2009; Coupar et al. 2012; Pollock et al. 2014; Winstein et al. 2016) would be superior to other types of rehabilitation therapy. Importantly, in a recent US multicenter trial, it was demonstrated that there were no differences in long-term functional outcomes between three different types of OT (Winstein et al. 2016).

A relatively recent discovery in motor rehabilitation is to use rTMS to modulate regional excitability of the motor cortex (Hummel and Cohen 2006) and to induce

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neuroplastic changes with the aim of enhancing the responsiveness to standard clinical therapy protocols. Inhibitory 1 Hz rTMS can be utilized to downregulate the nonlesioned hemisphere with the goal of improving response to motor training by reducing interhemispheric inhibition and potentially facilitating activity in the lesioned hemisphere. Two potential roles have been described for rTMS in stroke recovery: (1) inhibition, i.e., downregulation, of the nonlesioned side (using 1 Hz rTMS), or (2) excitation of the lesioned side (using 10 Hz rTMS or personally tuned alpha-frequency rTMS).

Stimulating the brain to drive its adaptive plastic potential seems to also accelerate the rehabilitative potential of task-oriented training in patients with paresis. So far, M1 has been invariably stimulated in all existing studies. Yet, we all may have overgeneralized its potential. Theoretically and empirically, M1 is indeed the optimal site for modulating the adaptive potential of a lesioned motor system, presuming that M1 has any viable tissue that has survived, i.e., neuronal reserve. In patients with serious lesions and impairments, M1 and its CST output may be damaged beyond repair, however. If M1 and CST are nonfunctional because of cell death, no neuromodulatory treatment can restore the original functions, and they must be bypassed.

- In such patients, the target for cortical stimulation should show a high probability of survival, a great number of descending projections, and an adaptive potential, which are required for recovery across the seriously impaired.
- For neuromodulation to promote motor recovery, such as to facilitate plasticity of alternate descending output, restore interhemispheric balance, and establish widespread connectivity bypassing the lesion, scientists may need to seek actively alternative sites for stimulation.
- Although at this time it is difficult to predict a substitute for M1 in a stratified group of patients, according to current knowledge, the site(s) must have causal interconnections reaching from cortical level to individual muscle innervation.

The current consensus from neuroimaging studies is that the best predictor of recovery of function is a return to a prelesion activation pattern, i.e., lateralization of activity to the primary cortical motor areas contralateral to the (paretic) limb (for a review, see Grefkes and Ward 2014). Even if stimulation of M1 may benefit those with maximum recovery potential, targeting novel neuromodulatory approaches to vicarious parts of the motor network may prove to be more effective than stimulating a single locus that is consistently ineffective in a given patient group.

14.2 Neuromodulatory TMS Concepts for Rehabilitation

Repeated TMS pulse trains in rTMS modulate cortical activity by either upregulating or downregulating cortical excitability depending on the rTMS parameters used. Delivering TMS pulses repetitively at frequencies of about 1 Hz leads to changes in cortical excitability that last well beyond the stimulation session. HF rTMS $\geq$3 Hz

leads to cortical excitation, as evidenced by increased amplitude of the TMS-induced MEPs (Pascual-Leone et al. 1994), whereas LF rTMS, that is, a pulse frequency of about 1 Hz, leads to cortical inhibition as evidenced by decreased amplitude of the TMS-induced MEP (Chen et al. 1997). This poststimulus cortical state is locally defined by net excitation or inhibition—however, the remote effects in the interconnected motor network may be the complete opposite.

Animal observations offer a possible explanation for opposing modulatory effects at high and low frequencies. Moliadze et al. (2003) stimulated the visual cortex of anesthetized cats with single-pulse TMS while recording time-locked neural activity with intracortical microelectrodes. Each TMS pulse caused an initial increase in neuronal activity for up to 500 ms followed by long-lasting suppression. The results suggested that stimulating with rTMS at frequencies >2 Hz for an extended period of time may keep neurons in an excitatory state, with each subsequent pulse reducing or masking the inhibitory phase of the preceding pulse. Conversely, stimulating at frequencies from 0.2 to 1 Hz may lead to cortical inhibition by favoring the manifestation of the long-lasting inhibitory phase.

The modulatory aftereffects of rTMS share many features of basic adaptive plasticity mechanisms, long-term potentiation (LTP), and long-term depression (LTD), leading to speculation about a similar cellular mechanism (Thickbroom 2007). The cellular processes that occur following rTMS are likely to include alterations in gene expression and neurotransmitter levels. Healthy rats chronically stimulated with 20 Hz rTMS for 10 s daily over 2 weeks showed increased c-Fos levels in the parietal cortex and hippocampus (Hausmann et al. 2000). In addition, rTMS-induced changes in levels of neurotransmitters such as glutamate and GABA may also contribute to modulatory aftereffects (Bolognini et al. 2009).

There is a plausible rationale for treating paretic patients with HF rTMS to the lesioned M1. The pivotal findings of Nudo et al. (1996) revealed that rehabilitative training of skilled hand use after focal cortical infarcts resulted in prevention of the otherwise frequent loss of hand territory adjacent to the infarct. In some instances, the hand representations expanded into regions formerly occupied by representations of the elbow and shoulder. Functional reorganization in the undamaged motor cortex was accompanied by behavioral recovery of skilled hand function. The authors suggested that after local damage to the motor cortex, rehabilitative training can shape subsequent reorganization in the adjacent intact cortex, and that the undamaged motor cortex may play an important role in motor recovery (Fig. 14.1).

Functional neuroimaging in stroke has revealed that neurons in the area of the lesioned M1 surrounding the injury often take over function in patients with good recovery (Zemke et al. 2003), a process sometimes called vicariation. In the acute period after a stroke, the activity in these perilesional neurons is reduced. Thus, excitatory HF rTMS may render perilesional neurons more responsive to therapy, speeding the process of transferring damaged function to the nearby neuronal structures. The same effect is gained naturally by unmasking M1 networks, which have the capacity to overtake damaged behavioral function.

The promising approach of contralesional inhibitory 1 Hz stimulation is based on interhemispheric connectivity. Application of LF rTMS to the contralesional M1

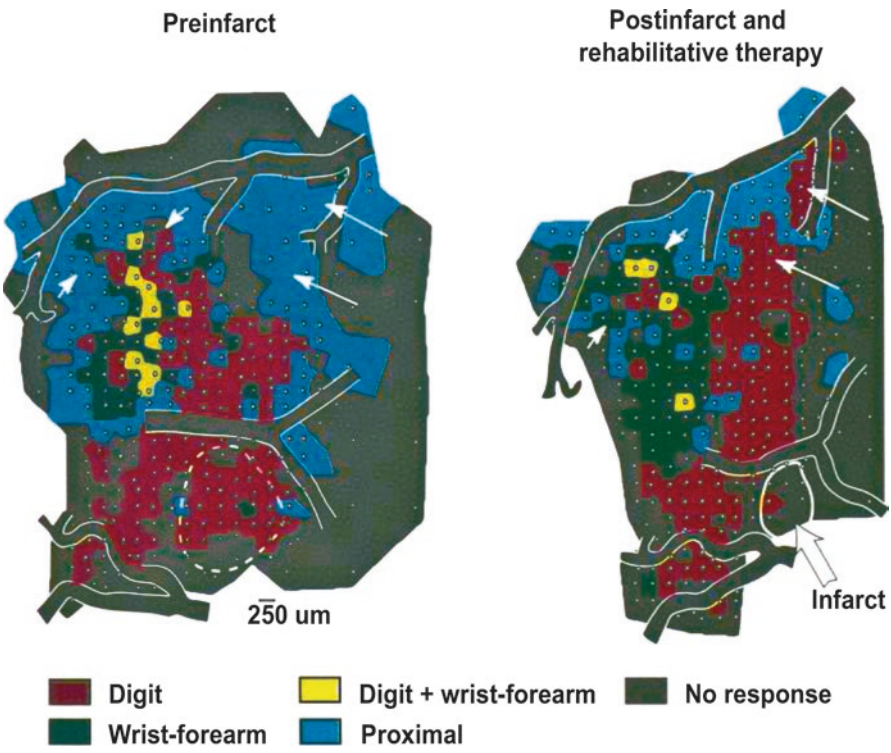

Fig. 14.1 Reorganization of hand representations in the primary motor cortex. Reorganization of hand representations in the primary motor cortex before infarct (*left*) and after a focal ischemic infarct and rehabilitative training (*right*). At each microelectrode penetration site (*small white dots*), intracortical microstimulation (ICMS) techniques were used to define movements evoked by near-threshold electrical stimulation. In this animal, the infarct destroyed 21.6% of digit and 4.1% of wrist-forearm representation. After infarct rehabilitative training, the spared digit representational area increased by 14.9% and the spared proximal wrist-forearm representational area increased by 58.5%. The *dashed circle* in the preinfarct map encompasses cortical territory targeted for ischemic infarct. The *large white arrow* in the postinfarct map indicates the infarcted region. The reduction in size of the infarcted zone is attributable to tissue necrosis during the rehabilitation period. *Long thin arrows* point to adjacent, undamaged cortex in which digit representations (*red*) appear to have invaded regions formerly occupied by representations of the elbow and shoulder (*blue*). *Short thin arrows* point to wrist-forearm representations (*green*) that appear to have invaded digit, elbow, and shoulder representations. (Adapted with permission of AAAS; Nudo RJ, Wise BM, SiFuentes F, Milliken GW. Neural substrates for the effects of rehabilitative training on motor recovery after ischemic infarct. Science. 1996; 272:1791–4)

may restore balance between the two cerebral hemispheres. In healthy individuals at rest, the motor cortices inhibit one another through transcallosal inhibition (TCI) (also termed interhemispheric inhibition; Ferbert et al. 1992). If one side is lesioned, modulatory inhibition to the other side is reduced, leading to increased activation in the nonlesioned side. The nonlesioned side still provides inhibitory signals to the lesioned side via the undamaged cortical system, even more than in the healthy

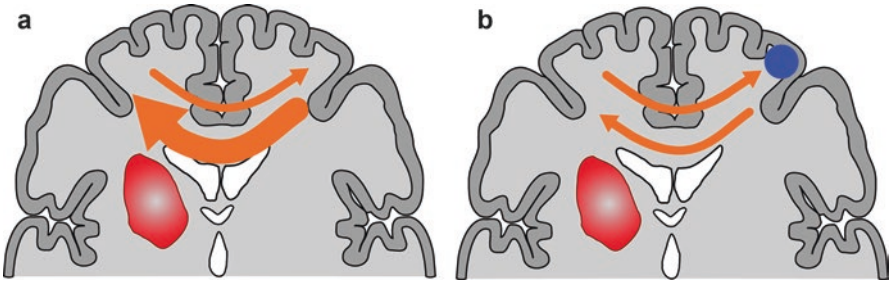

Fig. 14.2 Disrupted balance of inhibition between hemispheres. After CNS injury, the balance of inhibition between hemispheres is disrupted. (**a**) The excessive inhibition from the nonlesioned hemisphere is not controlled by the lesioned hemisphere and interferes with recovery of the lesioned side. (**b**) Inhibitory 1 Hz rTMS stimulation targeting the motor cortex of the healthy hemisphere normalizes the interhemispheric balance and facilitates the response of the lesioned side to subsequent motor training. Electric field navigation then facilitates accurate and consistent stimulation of the cortical representations of target muscles

balanced situation. Behaviorally, when healthy subjects perform unilateral limb movement, TCI from the ipsilateral hemisphere is released just prior to the activation of the limb (Murase et al. 2004), a mechanism that may promote more accurate unilateral movements. In the case of stroke, however, TCI from the contralesional M1 is not released with attempted limb movement, further impairing motor recovery (Grefkes et al. 2008).

Inhibitory modulation in the contralesional M1 with LF rTMS may lead to disinhibition, thereby restoring the balance between the two hemispheres and improving the opportunity for neuroplastic change in the perilesional M1. In general, the "release" of the motor system from an overall inhibitory state caused by a lesion or lesion-induced impaired or maladapted feedback, be it sensory or motor, seems beneficial to behavioral recovery (Fig. 14.2).

14.3 Current Status of Neuromodulation Studies in Rehabilitation

At least 27 studies on the effects of contralesional 1 Hz rTMS targeting the motor function of the primary motor cortex by utilizing varying rTMS protocols were performed in more than 2000 patients with stroke between 2005 and 2016. Further, in a recent meta-analysis of 18 randomized controlled trials including a total of 392 patients, rTMS therapy was found to have a positive effect on motor function in patients with stroke (Hsu et al. 2012). This meta-analysis found a significant effect size of 0.55 for motor outcome (95% CI 0.37–0.72). Further subgroup analyses demonstrated more prominent effects for subcortical stroke (mean effect size 0.73, 95% CI 0.44–1.02) and in studies that applied LF (1 Hz) rTMS (mean effect size 0.69, 95% CI 0.42–0.95). The meta-analysis concluded that rTMS has a positive effect on motor recovery in patients with stroke, especially for those with subcortical stroke.

14.4 Considering the Caveats in Current Rehabilitation Approaches

To date (the beginning of 2017), no published studies have been designed to demonstrate clinically relevant efficacy, and only some studies have combined rTMS with specific rehabilitation training. Importantly, the majority of studies have been performed with investigational rTMS devices without the aid of neuronavigation. Thus, therapy delivery has been performed "blindly," relying on observed motor responses. Device operators have not been able to confirm targeting of stimulation to a specific neuroanatomic site corresponding to the lesioned motor cortex and have not been able to monitor the stability of therapy delivery lasting several minutes.

14.4.1 Corticospinal Integrity Is Often Neglected

Since TMS does not require active participation of the subject, the method does not suffer from the confounding factors inherent in other functional brain imaging methods. Additionally, TMS can be performed equally well on paralyzed, sedated, or uncooperative patients in the clinical setting. The capability to noninvasively probe the cerebral cortex and corticospinal pathways allows applications ranging from (recently often neglected) straightforward diagnostic examinations to studies in which TMS is used for stratification of targets for rehabilitation.

TMS evokes motor responses, which are detectable by using EMG, and provides a unique paradigm for motor system imaging. Cortical stimulation evokes physiological responses, which can only be measured when there is a functioning cortex with intact tracts through the subcortical layers distally to the corresponding muscles. There is a causal relationship between cortical activation and muscle movement; in other words, the stimulated cortical patch is mandatory for tracing of movement. It is always easier to protect and reinforce a remaining and existing connection than it is to build a new one in the human brain.

14.4.2 Is a Paretic Limb Paretic?

Very recently, in a report comparing nTMS and nonnavigated TMS in detection of muscle responses in poorly performing chronic stroke patients, nTMS showed a significantly better rate of detecting cortically evoked MEPs in seemingly paretic arms (32 subjects with stroke with a median age of 62.5 years, 15 of whom were low functioning) (Active Arm Reaching Action Test [ARAT] = 0). Among the 15 low-functioning subjects, 5 (31.3%) had absent MEPs using both nTMS and TMS, 6 (37.5%) showed MEPs using both nTMS and standard TMS, and 5 (31.3%) showed MEPs using nTMS but not with standard TMS. There were no significant differences in amplitude or latency values between stimulation methods (Tanksley et al. 2017). However, in healthy adults, nTMS elicits MEPs with larger amplitudes and shorter latencies than nonnavigated TMS (Julkunen et al. 2009).

The authors (Tanksley et al. 2017) concluded that nTMS obtained MEPs in more muscles in a higher portion of low-functioning subjects compared to standard TMS, likely because of the increased precision offered by navigation and more systematic coverage of lesioned cortex and its surroundings. *Thus, "nTMS may be superior for assessing and/or predicting functional recovery after lesion, particularly in more severely impaired subjects"* (Tanksley et al. 2017).

14.4.3 Stratification of Patients for Neuromodulation by nTMS Mapping

There may be several reasons for the ability of nTMS to elicit a MEP among lower-functioning subjects compared with nonnavigated TMS. First, because the primary underlying reason is intersubject variation in rMT/MEP elicitation as a result of varying distance from the skull to the cortex (Julkunen et al. 2012), atrophies, which change this distance, need to be accounted for. Further, persons with severe impairment show increased activation and recruitment of secondary motor areas during functional task movements (Thickbroom et al. 2004), resulting in possible cortical motor map shifts (Nudo et al. 1996) and a subsequent decreased ability to find an MEP hotspot without navigation. Another potential reason for nTMS to elicit a more reliable MEP in lower-functioning subjects may be because it achieves a more accurate hotspot with which to start mapping; however, there are two reasons why this is unlikely. First, the hotspot rMT does not differ between navigated and non-navigated TMS, suggesting similar cortical activity (Julkunen et al. 2009). Second, differences in hotspot location have been observed for both low- and higher-functioning subjects, suggesting that the hotspot location may not be as important as the systematic precise mapping and the ability to visualize the functional anatomy online.

Because it is not possible to understand structural anatomy or functional representational changes purely from clinical observation, individual MRI guidance is advantageous over scalp site methods. For example, a large lesion encompassing the primary motor cortex is visible on the 3D render. This allows the investigator to systematically search lesion margins. Using a scalp-based grid in such a case with the same relative number of stimuli and experimental time has a higher probability of stimulating areas where no vital brain tissue resides at the effective TMS penetration depth.

14.4.4 Corticospinal Tract Plasticity

With spontaneous recovery from a cerebral lesion, CST and alternate output from the surviving motor cortices amplify (Lindenberg et al. 2010; Stinear et al. 2008), becoming more excitable, eliciting larger motor potentials in the paretic muscles, and involving output from additional, more extensive areas (Wittenberg et al. 2003). This premise is strengthened by evidence that with precentral stroke in primates, the

recovery of fine motor skills is supported by structural plasticity of the CST from the SMA (McNeal et al. 2010). In the case of a failing M1, CST from the PMC increases in responsiveness; for instance, following stimulation that inhibits M1 activity, responses from PMC become heightened (Schmidt et al. 2013).

However, in healthy primates, stimulation of PMC evokes spinal neural responses less frequently and spreads across fewer sets of upper-limb muscles than M1 (Boudrias et al. 2010; Zinger et al. 2013). Despite the prevalence of anatomic connections to the CST (Dum and Strick 1991), their connections to spinal neurons for distal muscles are less extensive than those from M1 (Zinger et al. 2013). Although, in healthy primates, corticospinal fibers of PMC are unable to directly activate spinal motor neurons dedicated to the finger muscles, evidence in injured primates shows that CST from the PMC may modulate CST plasticity (see above, McNeal et al. 2010; Zeiler et al. 2013).

14.4.5 Maladaptive Postlesion Spasticity

Spasticity following injury to the CNS has been attributed to a combination of disinhibited spinal reflexes and disbalanced cortical control of the affected limb (Brown 1994). Hyperexcitability of the lesioned sensorimotor cortex (Lindberg et al. 2009) would lead to a maladaptive end result of rTMS upon (a) too much excitatory rTMS, (b) wrong timing of rTMS (while patients recover limb function, activity returns to the lesioned hemisphere naturally (Carey et al. 2002); too much excitatory activity could result in increased spasticity), and (c) mistargeting the stimulation.

Alternatively, one might use current focal techniques such as nrTMS to target excitatory stimulation to specific areas of the lesioned M1 and inhibitory stimulation to areas suspected of involvement in cortical spasticity, such as Brodmann area (BA) 3b of S1 (Lindberg et al. 2009) or remote cortical areas that have become overactive due to network-level plastic changes. Future research could focus on restoring activity to the lesioned M1 while preventing the undesired cortical component of spasticity by altering the timing of brain stimulation. For example, research could examine the effects of coupling excitatory brain stimulation to the lesioned M1 in the acute period after stroke with inhibitory stimulation to the lesioned M1 and/or S1 in the subacute to chronic period as spasticity begins to develop.

Clearly, more longitudinal studies across the acute, subacute, and chronic stages of recovery are needed to investigate the temporal dynamics of structural connectivity changes in postlesion spasticity. This may be an important consideration for longitudinal studies mapping changes in cortical activity, as precise hotspot localization is crucial for accurate mapping. Further, precise location of the hotspot is critical when using rTMS, as the efficacy of this therapeutic technique relies on precise identification of individual muscle representations or focal brain regions. Indeed, a recent study revealed that LF nrTMS (compared with nonnavigated rTMS) increased the physiological and behavioral effects in M1, suggesting direct evidence that interhemispheric modulatory effects are increased by precise and consistent stimulation (Bashir et al. 2016).

14.5 Why Do We Need Individual Navigation of rTMS in Clinical Use of Neuromodulation?

Clinical applications of rTMS will place stringent requirements on the accuracy and repeatability of the chosen rTMS method. The size and shape of the head and brain, the distance between the stimulating coil and responding neuronal tissue, as well as the location and orientation of anatomical structures are all variables that will need to be defined individually for each patient; a standard coil location with respect to external landmarks of the skull is not sufficient or repeatable.

Anatomical measurements of in vivo brain macroscopic anatomy have shown that the anteroposterior variation in the location of the central sulcus with respect to the Talairach coordinate system is ±1.5–2 cm (Steinmetz et al. 1990), and the variation is likely to be significantly larger with respect to external skull landmarks. These findings indicate that macroanatomic individuality in the cerebral surface cannot be adequately accounted for by any proportional coordinates and certainly not by any morphometric landmarks (e.g., Cykowski et al. 2008). Individual sulcal patterns need to be used for evaluating and modulating functions when anatomical structures are smeared by brain pathologies, including tumors, edema, bleeding, and vascular alterations.

Even with easily recognizable individual anatomical landmarks, our ability to provide quantitative guidelines—for example, to functional somatotopic representations—is limited. One well-known landmark, the "*pli de passage fronto-pariétal moyen*" (PPFM) (Broca 1888), manifests as an elevation in the floor of the sulcus at its midpoint and is currently thought to localize the somatotopic hand area, which can often be clearly visualized as "omega," or the "hand knob" on the cortical surface (Yousry et al. 1997). However, no quantitative guidelines exist for the recognition of the PPFM relative to functional cortical representations in the central sulcus, and, indeed, we do not know the exact variation or the extent of the PMC and SMA even in healthy brains.

In addition to spatially accurate information on cortical representations, information on the rTMS "dose" is needed for neuromodulation approaches. Clearly, the strength of the stimulating magnetic pulse, a simple measurement expressed as a percentage of the maximum output of the machine, cannot account for the notoriously large individual variation in MEPs. The generally accepted method to determine the strength of a stimulus is to relate it to the rMT, which is measured individually for each patient, i.e., to the lowest stimulus intensity sufficient to activate a peripheral muscle when the stimulus is delivered to the presumed optimal cortical motor representation area of the muscle. However, in all lesioned patients, there are several practical caveats to this approach: (1) the optimal location of the stimulating coil is hard to define over the lesioned cortex, and (2) it is practically impossible to repeat without visual aids while measuring rMT. (3) The rMTs of different muscles, even neighboring ones, may differ, and, indeed, (4) the optimal muscle representations are shown and expected to move in and around lesioned motor cortical areas during recovery. (5) Additionally, the real strength of the stimulus reaching the cortex is completely unknown when targeting atrophied/edematic

motor cortical areas. As a consequence, the neuromodulatory rTMS may be ineffective if the stimulus intensity has been adjusted to a level around or slightly above the initially inaccurately defined threshold for motor responses.

Current methods of TMS or nTMS do not account for the anisotropic structural differences of cortical neuroanatomy. Hence, it is often assumed that rMT represents a general level of cortical excitability, enabling estimation of individual rTMS application intensity based on rMT at all cortical locations. This assumption causes the most uncertainty regarding the sufficiency of rTMS intensity at cortical locations at which immediate response cannot be detected, like in the prefrontal areas. In addition to the aforementioned list of practical caveats, the anisotropy of local neuronal organization may vary within the cortex. Theoretically speaking, TMS may activate neuronal axons at the bend or where they terminate (Ilmoniemi et al. 1999; Roth 1994). Considering that TMS requires activated neurons to be oriented appropriately with respect to the induced electric field—with neurons activating along rather than across it—then if several neurons are activated simultaneously, all the neurons need to be orientated appropriately in order to be activated by TMS. In this case, in a stimulated volume, neurons possess high structural anisotropy. However, such ideal structure is unlikely. Conditions such as cortical dysplasia and structural damage such as that caused by stroke are known to alter cortical structural anisotropy (Julkunen et al. 2016), meaning that neurons within a single volume of cortical tissue are not as prone to TMS due to the lower level of anisotropy. This may induce an apparent rise of rMT (Kallioniemi et al. 2015a, b). Hence, generalizing the association between cortical neuronal anisotropy and TMS-induced activation, high anisotropy may reflect high proneness to TMS, while low neuronal anisotropy will likely reflect low proneness to TMS activation. If the level of neuronal anisotropy changes when moving from one point to another within the cortex, the threshold level for TMS-induced activation will likely also change. This simplistic idea also will be prone to differences in the size of the TMS-activated neuronal populations.

Methodological factors may severely obscure the detection and quantification of underlying cortical loci and confound the clinical use of rTMS. Many of the fundamental issues can be resolved by using image-based navigation of stimulation according to the individual patient's brain anatomy. Optimal localization and orientation of stimuli with respect to the targeted anatomical structure, as well as maintaining the stimulus location stable in repeated delivery, may be a prerequisite for desired neuromodulatory effects to take place (Bashir et al. 2016).

14.6 The Method: Navigating the Electric Field in the Brain, Not the Device on the Scalp

Individual navigation and targeting solve many of the critical issues associated with the reproducibility and reliability of TMS in rehabilitation. Navigation combines data on anatomical structures with known delivery of stimulation, thereby forming the basis for dose determination and targeting. Despite the name "transcranial magnetic stimulation," the magnetic field itself that originates from the TMS coil has no direct effect on human neurons, whether delivered in single pulses or in neuromodulatory rTMS mode. Yet, TMS can directly affect the membrane potential of neurons.

The link, a principle law of nature, is that any time-varying magnetic field is always accompanied by an electric field (Chap. 1). While much of the literature uses the terms *electrical current* and *electric field* interchangeably, they are unequal: the electrical current is a by-product resulting when the electric field forces the movement of electrically charged ions in the tissue. An electric field can exist without an electrical current, for instance, where a cellular membrane prevents a flow of ions and hence prevents a current from flowing. The electric field can be closely estimated when the shape and size of the copper windings in the stimulating coil, the size and shape of the head, the electrical characteristics of the stimulator, and the exact location and orientation of the coil with respect to the head are known (Ravazzani et al. 1996; Ruohonen and Ilmoniemi 1999). Brain lesions do have a minor effect, but even then the prominent features of the electric field are determined primarily by the coil-to-head distance, coil orientation, and local skull shape.

14.7 Similarity of Electric Field nTMS to DES

At a conceptual level, nTMS creates "virtual electrodes" in the brain and can thereby stimulate individual neurons and neuronal populations. Indeed, the mechanisms of action are the same for both methods: a potential difference exerts a force in the tissue that tries to move electrical charges (particles, ions, molecules). Because the neuronal cell membrane is intrinsically sensitive to local changes in the electric potential along the path of the axon, wherever the electric field is of adequate strength and suitable direction, it will excite the neurons and trigger action potentials.

An electric field is required to excite neurons, and electrical and magnetic stimulation are essentially equivalent techniques of neuronal stimulation. In the case of electrodes placed directly in the brain, it is intuitive to assume, correctly, that the field is the strongest in the immediate vicinity of the electrodes. Yet, the spread of electric fields from the electrodes is very complex because the electric current (and field) will follow the paths of least impedance in the tissue, which is greatly influenced by macroscopic (e.g., sulci, cerebrospinal fluid) and microscopic factors (e.g., cortical layers, preferred orientation of cells, the length of neuronal projections) (Ruohonen and Karhu 2012). In TMS, the interaction is relatively simple: the magnetic field from the coil is perfectly undisturbed by any tissue variations. In each and every intracranial location, a magnetic field will generate (induce) a stimulating electric field. Macroscopic (e.g., skull shape) and microscopic (e.g., changes in resistivity along the path of the electric field) factors also affect the electric field in TMS, but the majority of the electric field is generated by the undisturbed primary magnetic field (Ruohonen and Ilmoniemi 2005). This is the main reason why TMS can be modeled precisely, perhaps more so than DES.

14.8 Basic Physiology for Motor Network Neuromodulation

For electrical stimulation, it has been historically established that neurons are excited at lower thresholds when applied voltages induce currents oriented longitudinally along the axon rather than transversely across the axon (Day et al. 1989;

Ranck 1975; Rushton 1927). Electrical stimulation has been found most effective when the applied current has the same orientation and timing as the normal flow of postsynaptic current during depolarization: from the dendrites through the soma to the axon. Early TMS studies suggested that the threshold for excitation is sensitive to orientation (Brasil-Neto et al. 1992), with optimal responses achieved when the induced current is oriented 45° medial to the anteroposterior plane. Although early TMS studies used no navigation method to confirm the underlying surface anatomy, the orientation was interpreted to indicate that optimal stimulation of M1 was achieved when the induced current was perpendicular to the central sulcus, as was subsequently confirmed in many later studies.

TMS coils are flat and placed tangentially to the scalp; the induced electric field is also tangential to the scalp. Hence, at the crown of the gyri, the electric field is in the plane horizontal to the radial alignment of the cortical columns. Accordingly, Day et al. (1989) hypothesized that TMS stimulation must excite the tangentially oriented neural elements at the gyral crown, such as horizontal interneurons or horizontal collaterals of pyramidal tract axons, since the proximity to the coil outweighs all other factors. As sensitive as the electric field in the brain is to the distance between the coil and the targeted area, this assumption clearly disagrees with the clear orientation selectivity observed by Brasil-Neto et al. (1992) and Mills et al. (1992). Horizontal fibers extend uniformly in all directions within a plane parallel to the cortical surface, so the induced electric field should excite an equivalent fraction of the fiber population in any orientation.

However, the clear sensitivity of single-pulse nTMS responses to the orientation of the coil (Kallioniemi et al. 2015a, b; Schmidt et al. 2009) suggests that the predominant activation mechanisms are related to the trajectories of pyramidal tract axons and the direction along the cortical columns, as verified in recent studies and comparisons with intracranial DES (Picht et al. 2009a, b; Krieg et al. 2012). Suprathreshold stimulation may obviously lead to a combined activation of transsynaptic pathways and direct stimulation of the axonal pathways deeper in the gray matter or in the bending/tapering of white matter structures. When the TMS-induced electric field causes sufficient membrane depolarization, action potentials are generated in the entire stimulated neuronal volume, leading to synaptic transmission and excitatory or inhibitory postsynaptic potentials (EPSPs or IPSPs, respectively). Physiological principles imply that nTMS is most effectively applied by orienting the electric field to be longitudinal and orthodromic to the greatest possible number of neurons at the site of interest.

14.9 Clinical Results Obtained with Electric Field Navigation

The individual clinical accuracy of electric field navigation has been validated in studies comparing nTMS to intraoperative DES in patients undergoing neurosurgery. The mean distance between nTMS and DES reported in six publications was 6.18 mm in 81 patients (Takahashi et al. 2013). This level of spatial accuracy may overcome the clinical problems of targeting TMS to individually lesioned cortex and, in particular, the repeatability required for day-to-day post-injury therapy.

In healthy subjects and in patients with chronic stroke, the effects of 1 Hz rTMS were greater when nrTMS was used to target an optimal cortical location in M1 (Bashir et al. 2011, 2016). Further, in a recent 30-patient phase II clinical trial, 84% of patients with subacute stroke receiving 1 Hz contralesional nrTMS as adjunct to task-oriented rehabilitation attained clinically important improvement of at least 5 points on the upper extremity Fugl-Meyer scale, whereas 50% did so in the sham-nrTMS group (Fig. 14.3; Harvey et al. 2014).

We have quoted in a separate chapter on plasticity in this volume (Chap. 16) a classic Hebbian principle: Hebb described plasticity using the example of two adjacent neurons that could take part in firing each other, with the efficiency of the firing cells increasing as a consequence of some growth process or metabolic change (Hebb 1949). The original formulation is nowadays often described "what fires together, wires together." Notwithstanding the wording, Hebb's principle describes elegantly the principle of network synaptic plasticity. Moreover, it fulfills the basic empirical requirements for LTP, which is the best-known and most studied adaptive neuronal mechanism of the mammalian brain. Current protocols for neuromodulation in treatment of paresis lean heavily on the principle of adaptive plasticity in the

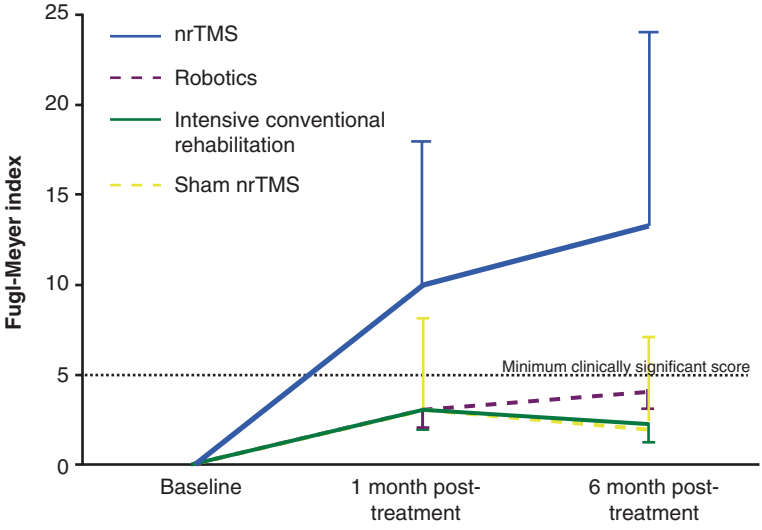

Fig. 14.3 Improvement in Fugl-Meyer score after contralesional 1 Hz nrTMS followed by occupational therapy. In this study, 29 stroke patients with subacute stroke (3–9 months poststroke with incomplete recovery) were randomly assigned to an active group (19 patients, who received 1 Hz nrTMS targeted to the wrist extensor representation in the nonlesioned hemisphere followed by occupational therapy (OT)) or a sham group (ten patients, who did not receive TMS treatment but otherwise went through the same experience, cf. Fig. 14.2). Following baseline assessments of function and excitability, the subjects completed three visits per week for 6 weeks that included 20 min of prefunctional OT, 1 Hz nrTMS, and 60 min upper-limb task-oriented OT. Subjects returned for 1-week, 1-month, and 6-month follow-up visits. Out of the group receiving nrTMS treatment, 84% showed clinically important improvement (over 4.5 points in Fugl-Meyer score). Harvey et al. Stroke 2014;45:A152, Robot-assisted therapy for long-term upper-limb impairment after stroke. Lo et al. N Engl J Med. 2010 May 13;362(19):1772–83

human motor system. When attempting to drive neuromodulation in the motor network, it is critical that nrTMS is stable and repeatable from day to day to gain behavioral benefits (Bashir et al. 2011, 2016).

14.10 Alternative Stimulation Strategies for Paresis Therapy

14.10.1 Targeting Nonprimary Motor Areas (Areas Outside M1) for Therapeutic Neuromodulation

As discussed earlier in this chapter, spontaneous remapping of periinfarct M1 in post-injury recovery was a finding that largely steered approaches in neurorehabilitation in recent decades (Nudo et al. 1996). However, animal models show that even when a majority of hand representation of M1 is destroyed, PMC can remap its representation by almost 50% (Frost et al. 2003). Functional neuroimaging supports evidence for premotor remapping in humans. Ipsilesional PMC activates during movements of the paretic hand, and this activation increases proportionally to the damage to M1 and its CST (Ward et al. 2007). The adaptive remapping of the PMC is believed to be a product of their anatomic substrates, which include direct functional and anatomic connections to individual muscles, "alternate CST" (Liu and Rouiller 1999, Teitti et al. 2008, Vaalto et al. 2011), and flexible somatotopic organization (Cunningham et al. 2013).

In nonhuman primates, it has been demonstrated that following a complete lesion to the M1's hand representation, the PMC's hand representations, rather than non-hand territories in perilesional M1, may be remapped (Liu and Rouiller 1999). TMS applied to the ipsilesional dorsal premotor cortex (PMd) delays the reaction time of moving the paretic finger (Fridman et al. 2004) in patients with infarcts of M1 or CST. Delays can be induced when contralesional PMd is inactivated (Johansen-Berg et al. 2002).

Premotor areas contain organized neuronal components, which may compensate for lesioned M1 and CST, in particular in the most behaviorally impaired patients. The exact target for modulatory nTMS is as yet untested. A promising candidate may be a nonprimary cortical area (such as M2), which is activated by nTMS and has an alternate, direct CST providing a functional route to peripheral muscles at the same MEP latencies as M1 proper (Teitti et al. 2008, Vaalto et al. 2011). More remote but densely interconnected areas of the intraparietal sulcus may also be a candidate to suppress for reduction of—possibly maladaptive—sensory information (Fig. 14.4).

14.10.2 Spinal Paired Associative Stimulation

PAS is a technique where TMS is synchronized with peripheral nerve stimulation (PNS). Initially, the ISI between orthodromic and antidromic signals has been timed individually to coincide at synapses at the cortical level to enhance CSE (Stefan et al. 2000). In spinal PAS, signals are timed to coincide at the spinal cord level

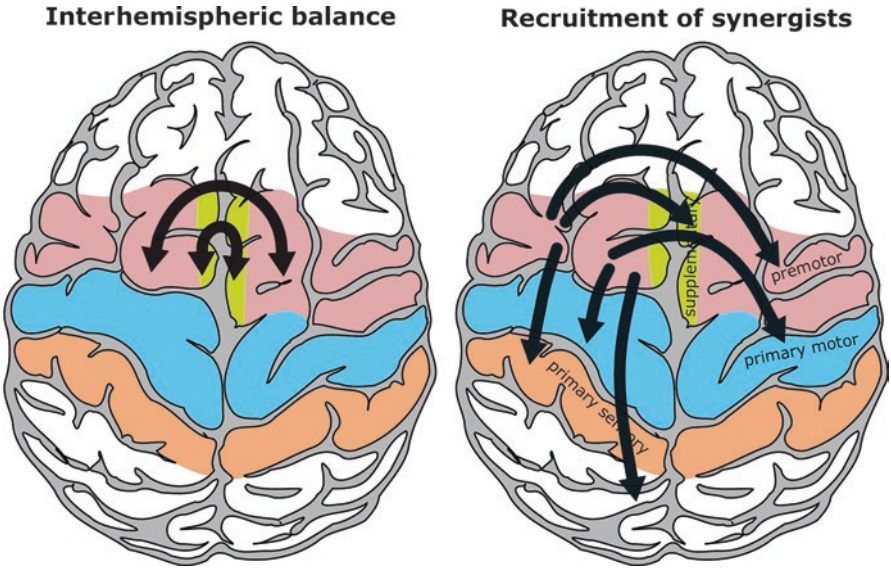

Fig. 14.4 Premotor areas—an alternative target for nrTMS? PMC (purple, lateral premotor areas; green, SMA; and cingulate motor area, which is not visible). PMC constitutes more than 60% of the frontal cortex that project to the spinal cord. The medial wall, such as the SMA and medial PMC, receives arterial supply from a source that is different from the most commonly infarcted middle cerebral artery that supplies M1. Thus, PMC would have a greater probability of survival than M1. PMC has neuroanatomical and physiological connective substrates for modulating (1) corticospinal plasticity, (2) the return of balance between the excitability of the ipsilesional and contralesional motor regions, and (3) vicarious recruitment of widespread frontal and parietal synergistic regions. PMC has direct, parallel output to the spinal cord, independent of M1. In stroke, their CST can exhibit plasticity via axonal sprouting and/or cortico-cortical facilitation of the CST from M1. PMC also possesses abundant callosal connections, both homotopic and heterotopic, which are far more extensive than between M1 and its homologue, and extensive functional connectivity with the ipsilateral posterior parietal cortex

(Cortes et al. 2011; Shulga et al. 2016a, b). A significant drawback of PAS is that to facilitate long-term rehabilitation, the initially calculated ISI needs to be adjusted constantly because CST integrity changes upon recovery from the injury. Moreover, the remaining neural pathways in patients with neurological diseases may have a wide range of conductivities as a result of partial injuries, making the determination of exact PAS timing impossible.

A recently arisen strategy is to increase the number of interactions between pre- and postsynaptic volleys through the increase of volley number, when LTP-inducing and LTD-inducing timing interactions occur at the same time. The increase in the number of orthodromic volleys can be achieved by increasing TMS intensity; high-intensity TMS pulses result in a repetitive HF discharge of corticospinal neurons (Di Lazzaro et al. 2008). To increase the number of antidromic volleys, HF trains of PNS can be used. Such protocols could theoretically enhance corticospinal transmission at a wide range of ISIs.

Spike-timing-dependent plasticity (STDP) is dependent on numerous factors: the firing rate, the number of coactive synaptic inputs, the state (voltage) in postsynaptic network voltage and the timing of the inputs, among others (Feldman 2012). Promisingly for practical clinical use in neurorehabilitation, it has been shown in vitro that spike-timing relationships causing LTP can "win" out over those favoring LTD when multiple interactions occur at the same time (Sjöström et al. 2001). In line with speculations, a recent case report of two incomplete spinal cord injury patients shows preliminary positive long-term effect of multiple-session spinal PAS consisting of single high-intensity TMS pulses combined with 50 Hz PNS trains (Shulga et al. 2016b).

14.10.3 Theta-Burst (50 Hz) Stimulation

Most of the studies of lesioned brain/stroke that were described earlier in this chapter have been conceptually more or less identical to the attempts to advocate motor recovery with TBS (for a review, see Suppa et al. 2016). They are based on a simple but functioning concept of a disbalanced interhemispheric equilibrium with (1) decreased excitability in the ipsilesional hemisphere, (2) increased excitability in the contralesional hemisphere, and (3) exaggerated inhibitory control from the contra- to ipsilesional hemisphere (Ward and Cohen 2004). TBS studies have demonstrated exactly the same concept that increasing the excitability of the Ipsilesional theta-burst stimulation (iTBS; presumably inducing LTD-like phenomena in primary motor networks) or depressing the excitability of the Contralesional theta-burst stimulation (cTBS; presumably causing predominantly LTP-like effects, but depending on the amount of stimulation) can improve motor skill and motor learning when applied concurrently with motor practice. It was initially thought that TBS produces more powerful and reproducible effects than other rTMS methods in less time, which has unfortunately not been proven to date.

Training of paretic-hand grip-lift kinetics improved after priming (15 min earlier) with iTBS of ipsilesional M1 or cTBS of contralesional M1 and deteriorated after sham TBS in subcortical chronic stroke patients (Ackerley et al. 2014). Somewhat discouragingly, though, priming TBS is ineffective for modifying M1 plasticity in older adults, which may limit the therapeutic use of priming stimulation in neurological conditions common in the elderly.

How to harness the quite recently coined term "metaplasticity" in brain lesions with disordered network activity is being currently extensively studied in the context of cerebral stroke. Metaplasticity is defined as modification of the direction, magnitude, and/or duration of plasticity by previous activity in the same postsynaptic neuron or neural network (Abraham 2008). It is often described in terms of plasticity at any given synapse being bidirectional, i.e., LTP or LTD can be induced, and it has been noted that the likelihood for LTP/LTD induction is not stable over time but depends homeostatically on the activity history of the postsynaptic neuron. Work from animal experiments demonstrates that metaplasticity plays significant

roles in the regulation of network function and behavior. A number of studies have examined metaplasticity processes tested by subsequent TBS protocols applied to M1; however, so far none of these have shown clinically relevant data. However, the concept of metaplasticity provides a theoretical framework for the "action-locked" or "closed loop" approaches to TMS-driven plasticity and, consequently, neuromodulation.

14.10.4 Brain State and Action-Driven TMS: Closed Loop

One possible origin of the variability in the response to brain stimulation such as TMS is the variability of instantaneous brain state at the time of stimulation (Ridding and Ziemann 2010). The best known and most widely used measure of brain states and their alterations at the neuronal network level is EEG, which can reach microsecond-level temporal accuracy, sufficient for following the ongoing neuronal signal processing in the brain. EEG and its magnetic counterpart, MEG, have characterized the 10-Hz-spontaneous oscillatory activity to be modality specific, with separate components for visual, sensorimotor, and auditory oscillatory thalamocortical neuronal loops. The sensorimotor μ-rhythm was originally characterized by Gastaut (1952), localized in the Rolandic area with 10 and 20 Hz components, and verified with MEG recordings to contain predominantly sensory and motor components with different reactivity (Karhu et al. 1994). For characterizing the ongoing state of sensorimotor system most relevant to the current discussion, the 10 Hz μ-rhythm is a readily and noninvasively available brain state biomarker. The potential of noninvasive closed-loop brain stimulation has been enabled by the combination of EEG and TMS (Ilmoniemi et al. 1997; Ilmoniemi and Kičić 2010) and the recent availability of low-cost real-time processor solutions. Considering the EEG signal conceptually as a lower-dimensional projection of instantaneous brain state, application of a TMS/nTMS pulse may be triggered, e.g., in the spontaneous (or motor-activity-induced) oscillatory phase that elicits the strongest LTP/LTD type of neuromodulatory effect. In other words, external stimulation occurs during the momentary, local brain state, and the effects of external TMS stimulus (or a stimulus train) reach the neural network when it is most receptive to reinforcement of existing functional connections or construction of new ones.

Noninvasive brain stimulation or behavioral neurofeedback can thus be coupled to endogenous brain activity in functionally defined brain networks in real time. For treatment of paresis, this "neurofeedback" allows:

1. Personalized neuromodulation in various states of the individual's sensorimotor network.
2. Accounting for the time course of dynamic changes during network reorganization, such as during stroke rehabilitation (Grefkes and Ward 2013). In these conditions, neurons and networks are modified as a function of their recent activity (metaplasticity), which may critically determine the direction, extent, and duration of neuromodulatory effects of TMS (Müller-Dahlhaus and Ziemann 2015).

14.11 Conclusion

The ultimate goal of adjuvant therapies in paresis treatment, such as nTMS, is to provide an optimally receptive neuronal environment in which natural recovery can happen and behavioral therapies can be imparted. In practice, most methodological problems concern:

- Minimizing the inaccuracies in dosing and targeting rTMS delivery
- Keeping the neuromodulatory rTMS stable over time and from day to day

At the moment, these individual stimulus delivery problems can be significantly alleviated by utilizing nTMS. What is needed for furthering the field of neuromodulatory therapies is:

- Stratification of patients and patient groups by functional biomarkers of lesions
- Seeking and testing cortical representations of the most beneficial targets and means of nrTMS when individual anatomy is unclear or does not provide reliable landmarks that would explain observed behavioral deficits
- Promotion of unorthodox approaches in the treatment of paresis, as relatively little is known about the effects of neuromodulatory rTMS at the network level

Multicenter projects concentrating on stratified patient groups and a priori agreements on test protocols are sorely needed. We must gain large enough comparable datasets for implementing neuromodulation as an integral part of the much neglected clinical neurorehabilitation.

In February 1962, Abraham Kaplan, a professor of philosophy at the UCLA, gave a banquet speech at the conference of the American Educational Research Association. The following excerpt about the speech included the earliest strong match for the currently well-known adage: Kaplan urged that scientists exercise good judgment in the selection of appropriate methods for their research. Just because certain methods happen to be handy or a given individual has been trained to use a specific method that is no assurance that the method is appropriate for all problems. He cited then Kaplan's law of the instrument: "Give a boy a hammer and everything he meets has to be pounded." Now may be the time for rehabilitation.

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Part VI

Further Potential of nTMS

The Potential of nTMS/EEG: Measuring Consciousness

15

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15.1 The Pitfalls of Behavior-Based Clinical Evaluation of Consciousness

Brain injuries of traumatic, vascular, or anoxic etiology differently affect sensory, motor, and cognitive functions. The spatial extent of the lesion and the specific involvement of key neuronal structures may ultimately lead to disorders of consciousness (DOC). Usually, after an acute brain insult, a patient is kept sedated for a short period (days to weeks) in order to recover stability of clinical parameters. When sedative drugs are withdrawn, the comatose state can usually end, and the clinical conditions of the patient may naturally evolve toward (1) a gradual recovery of behavioral responsiveness over time (with varying degree of sensory, motor, and cognitive disabilities) and (2) a chronic DOC. In this last case, patients are coarsely diagnosed as vegetative state (VS) if they can only provide reflexive responses to stimulation or as minimally conscious state (MCS) if they can perform inconsistent but reproducible voluntary movements (Giacino et al. 2002). This diagnostic

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distinction is performed by applying neuropsychological scales, such as the Coma Recovery Scale-Revised (CRS-R), which evaluates the patient's ability to provide appropriate behavioral motor responses to standardized sensory and cognitive stimulation (Giacino et al. 2004).

The quality of life of brain-injured patients with disorders of consciousness greatly depends on their ability to interact with the environment and to produce behavioral responses to sensory stimulation. However, a patient may be conscious but unable to signal it behaviorally (Laureys and Schiff 2012; Fernández-Espejo and Owen 2013) because of (1) sensory impairments that may hamper the perception of exogenous stimuli (Sanders et al. 2012), (2) motor deficits that limit the range of behavioral responses to stimulation (Fernández-Espejo et al. 2015), and (3) more complex executive functions or aphasic impairments that may result in a lack of motivation, of movement initiation, or in the inability to produce meaningful sounds/words (Schiff 2010). Consciousness and behavioral responsiveness may be dissociated also in healthy subjects, e.g., during dreaming (Stickgold et al. 2001) and some form of anesthesia (Domino 2010). Therefore, in general evaluating severely brain-injured patients from their ability to demonstrate subjective experience through motor behavior can be misleading (Sanders et al. 2016) as the absence of behavioral signs of consciousness per se cannot be considered a proof of the absence of consciousness. This is particularly relevant in the case of covertly conscious patients that may be misdiagnosed as VS (Majerus et al. 2005).

15.2 An Objective Brain-Based Approach to Consciousness

In order to improve the diagnostic approach to DOC patients, consciousness should be ideally evaluated with a brain-based measure that is independent of sensory processing, motor outputs, and subject's participation. Phenomenology suggests that each conscious experience is unitary (i.e., an integrated whole) and rich of information (i.e., with highly differentiated characteristics) at the same time. Integration is lost when a system can be separated into independent clusters of elements, while differentiation is lost when all the elements of a system are identically interconnected. Thus, in the brain, consciousness has been related to the ability of many functionally specialized thalamocortical modules (functional specialization) to interact rapidly and effectively (functional integration) (Friston 2002). A viable method to investigate the internal structure of the brain is by measuring its responses to a direct perturbation: a response confined to the stimulated site would suggest a loss of integration, while a response uniformly spreading over the whole cortex would indicate a loss of differentiation. In these cases, brain response will be either local or global but simple. Alternatively, a response that is early generated nearby the stimulated site and that progressively activates farther cortical regions with a highly specific pattern

of activation would represent an optimal balance between information and integration. In this case, the brain response will be spatiotemporally complex (Tononi 2004; Tononi et al. 2016).

This theoretical perturb-and-measure approach can be implemented through nTMS/EEG. This technique has the unique advantage of measuring with an excellent temporal resolution the neurophysiological responses of the whole brain to a direct, noninvasive stimulation of a selected cortical target. As such, nTMS/EEG is particularly useful in the case of brain-injured patients, since it bypasses sensory pathways, is independent from the integrity of motor output, and does not require a direct subject's participation. Using this technique, a novel metric—the perturbational complexity index (PCI)—has been recently developed (Casali et al. 2013) to approximate the amount of information contained in the integrated response of the thalamocortical system to a direct perturbation. The computation of PCI requires the estimation of the deterministic pattern of brain response to nTMS. First, a physical and geometrical model of the head is built from anatomical magnetic resonance images in order to estimate the current density distribution on the cortical surface that most likely generated the nTMS-evoked potentials recorded from the scalp. Then, a bootstrap-based data-driven statistical analysis is applied to extract the spatiotemporal pattern of cortical sources that have been significantly activated by nTMS. Finally, PCI is obtained as the Lempel-Ziv complexity of the matrix of significant cortical source activity, normalized by source entropy. PCI ranges between 0 (minimum complexity) and 1 (maximum complexity) and can be set to 0 when cortical neurons fail to engage in any significant activation pattern in response to nTMS perturbation.

15.3 Technical Setup and Stimulation Protocols

The simultaneous recording of EEG during nTMS engenders technical issues mainly related to the electromagnetic artifact produced by unwanted induction of current flow into the electrodes, which generates a signal considerably beyond the typical range of the EEG amplifier. The brief TMS pulse (about 200 μs) may saturate the EEG amplifier for several seconds, thus completely masking the immediate brain response to direct stimulation, which is essentially shorter than 500 ms. One approach to overcome this issue is to pause the amplifier just before the TMS pulse and restart the recording right after stimulation (sample-and-hold circuit; Virtanen et al. 1999). Another approach would be to increase the dynamic range of the amplifier in order to prevent saturation and to enlarge the bandwidth of the acquisition filter in order to reduce the distortion of the artifact. However, this approach necessarily requires a high sampling rate and a proper reduction of the electromagnetic artifact during data processing.

The validation study described in this chapter has been performed using a combination of nTMS and high-density EEG (60 recording channels) that implements

the sample-and-hold approach (Nexstim Plc, Helsinki, Finland). This system has the advantage of being integrated with an accurate nTMS system, equipped with a 3D infrared camera, which allows (1) to select an anatomical target on individual MRI; (2) to display in real time the location, intensity, and direction of the estimated electric field induced on the cortical surface; and (3) to monitor online and reliably reproduce across sessions the stimulation parameters. Concerning stimulation parameters, nTMS was delivered at a randomly jittered ISI of 2000–2300 ms bilaterally within the middle-caudal portion of the SFG (BA6 and BA8) and within the superior parietal lobule (BA7), about 1 cm lateral to the midline. These targets are involved in a cortical network that was suggested to be relevant for consciousness (Laureys et al. 1999; Di Perri et al. 2014; Fridman et al. 2014) and are far from the insertion of scalp muscles which may induce TMS-related artifacts (Mutanen et al. 2013). Each eligible cortical target was stimulated with an estimated electric field, orthogonal to the gyral crown, of about 120 V/m, which is usually above the neuronal activation threshold. In brain-injured patients nTMS pulses were delivered far from anatomical cortical lesions because, in these cases, nTMS is ineffective and does not evoke measureable responses (Gosseries et al. 2015). Whenever the stimulation of an apparently preserved cortical area did not produce any measurable brain reaction to nTMS, stimulation intensity was increased up to 160 V/m.

15.4 A Two-Step Validation of a Novel Metric of Consciousness

PCI has been shown to reliably distinguish between consciousness and unconsciousness in a reduced sample of subjects (Casali et al. 2013). An extensive validation is needed to propose its application in the clinical setting. However, the validation of this index, as well as of any brain-based measure of consciousness, is challenging because of a problem of logic circularity: since behavior-based clinical diagnosis may fail to recognize brain-injured patients who are conscious but disconnected and unresponsive, the true state of affairs necessary to define the accuracy and the optimal cutoff for a given brain-based measure of consciousness remains unknown (Harrison and Connolly 2013; Peterson et al. 2015).

To overcome this circularity issue, in a recent study (Casarotto et al. 2016), both immediate and delayed subjective reports have been collected as a reliable surrogate measure of consciousness (Noreika et al. 2011; Sanders et al. 2016) in a large benchmark population of 150 individuals, including (1) healthy subjects of different age (range 18–80 years) and conscious brain-injured patients who were awake and able to communicate; (2) unresponsive subjects who reported no conscious experience upon awakening from non-rapid eye movement (NREM) sleep or midazolam, xenon, and propofol anesthesia; and (3) subjects who were disconnected and

unresponsive during rapid eye movement (REM) sleep and ketamine anesthesia but retrospectively reported having had vivid conscious experiences upon awakening. For each individual, the maximum PCI value (PCI_{max}) obtained from the stimulation of different cortical sites was then considered for classification purposes: PCI_{max} was invariably higher in the conscious conditions (i.e., wakefulness in healthy subjects as well as stroke, emergence from MCS and locked-in syndrome patients; REM sleep and ketamine anesthesia in healthy subjects) as compared to the unconscious (i.e., NREM sleep and midazolam, xenon, and propofol anesthesia) conditions. Therefore, PCI_{max} values computed from this benchmark population allowed obtaining an empirical PCI cutoff (PCI*) that discriminated with 100% accuracy between conscious and unconscious conditions, irrespectively of connectedness, responsiveness, and presence of brain lesions.

Including brain-injured, yet conscious, patients in this benchmark population allowed evaluating PCI performances in individuals with substantial anatomical abnormalities of different kind and extent. This test is valuable because PCI is eventually aimed at assessing DOC patients, who are by definition characterized by severe brain lesions. Interestingly, PCI was somewhat sensitive to the overall lesion load of brain-injured patients: indeed, at the group level, PCI_{max} was significantly lower in conscious brain-injured patients including locked-in syndrome (LIS) (resulting from a vascular brainstem damage), stroke (ischemic or hemorrhagic cortico-subcortical damage), and EMCS (patients with a previous MCS of different etiology that partly recovered the ability to communicate and interact) as compared to healthy awake subjects. In spite of this, it was still possible to find an optimal cutoff PCI* that was able to perfectly distinguish between unconsciousness on one side and consciousness, even if disconnected, on the other. However, this cohort of brain-injured patients did not allow inferring about the functional role of specific brain networks for consciousness, because of their different etiology and because of heterogeneity of the anatomical lesions concerning both the extent and spatial location. Therefore, what are the minimal anatomical and functional requirements to sustain complexity within the brain is still an open question, especially for unresponsive patients in whom severe brain damage spares the function of large brain islands (Gosseries et al. 2014).

15.5 Clinical Application of PCI in Disorders of Consciousness

After being validated in a benchmark population, PCI was computed from 38 MCS and 43 VS patients. In this population, cortical targets were carefully selected on individual structural MRI in order to avoid brain lesions, on which nTMS is ineffective and does not evoke measureable EEG responses (Gosseries et al. 2015). Considering PCI* as an empirical cutoff, 36 out of 38 MCS patients resulted in PCI_{max} higher than PCI*, indicating that PCI has an unprecedented

sensitivity (94.7%) to detect patients who show minimal behavioral signs of consciousness.

The evaluation of VS patients represents a remarkable challenge, because in this category, behavioral responsiveness is apparently absent or unreliable and cannot provide any validation of the results obtained with nTMS/EEG. PCI_{max} has shown an extremely high sensitivity in detecting consciousness, even if disconnected, not only in healthy subjects but also in severely brain-injured patients, including MCS patients who show fluctuating behavioral responsiveness. This result implies that, in the lack of a ground truth, one could apply the independently validated PCI* cutoff to evaluate the VS population without running into a circularity issue. Thus, the computation of PCI_{max} in VS patients provided a physiopathological stratification of this clinical category into (1) a "no-response" subgroup in which nTMS targeted over different cortical areas failed to engage any significant cortical response ($PCI_{max} = 0$); (2) a "low-complexity" subgroup, in which nTMS triggered a local and stereotypical positive-negative response, similar to the one observed in healthy controls during unconscious NREM sleep and anesthesia ($PCI_{max} < PCI^*$); and (3) a "high-complexity" subgroup, in which nTMS engaged a rapidly changing and spatially differentiated cortical response, similar to the one observed in MCS patients and in responsive (wakefulness) or unresponsive (REM sleep and ketamine anesthesia) conscious controls ($PCI_{max} > PCI^*$). This physiopathological stratification may have several important consequences on the ethical and therapeutic management of DOC patients. Ethical issues suggest that no-response patients should be further investigated in search for preserved cortical and subcortical metabolic activations (e.g., by using PET imaging) that may have escaped the nTMS probing. Low-complexity patients may be directed toward drug neuromodulation with medications or brain stimulation techniques aimed at restoring consciousness and complex patterns of activity (Fridman and Schiff 2014). Finally, high-complexity VS patients, whose potentiality for consciousness is already shown by their pattern of EEG responses to nTMS (Fig. 15.1), should be selected for intensive interventions aimed at restoring responsiveness to the external environment, such as by increasing behavioral output through thalamic stimulations (Schiff et al. 2007) or by establishing communication through active paradigms or brain-machine interface (Naci et al. 2012; Chatelle et al. 2012).

In addition to disorders of consciousness, nTMS/EEG has interesting applications also in the field of epilepsy. Since epilepsy is commonly characterized by a general increase in cortical excitability, nTMS/EEG has been recently employed to measure and monitor cortical excitability in epileptic patients. Preliminary results (Valentin et al. 2008) are promising and suggest that nTMS/EEG could be potentially applied to better characterize and monitor the excitability changes occurring in focal cortical epileptogenic lesions during antiepileptic drug therapy withdrawal/modification or during neurostimulation treatment.

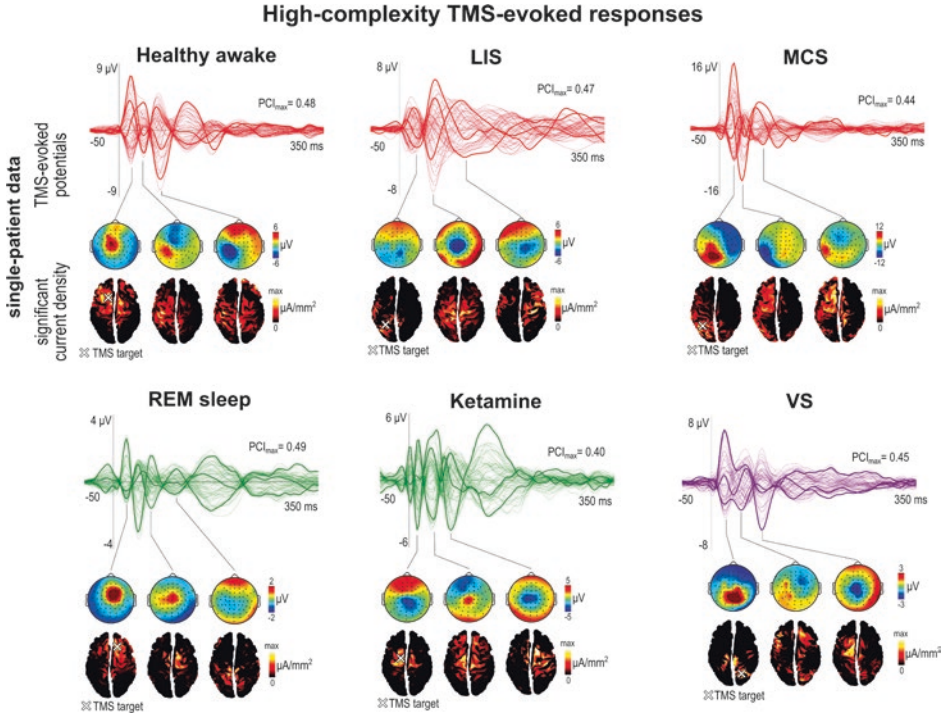

Fig. 15.1 Examples of nTMS/EEG recordings for measuring consciousness. In each panel, average nTMS-evoked potentials (all channels superimposed, with three illustrative channels highlighted in *bold*) together with the PCI_{max} values. Three voltage scalp topographies and significant current density cortical maps are shown at selected time points. *Red traces* indicate individuals who may show behavioral responsiveness during nTMS/EEG recording (healthy awake subjects, LIS, and MCS patients). *Green traces* indicate healthy individuals who are in a state of disconnected consciousness, i.e., behaviorally unresponsive during the experiment but able to report dreamlike conscious experiences upon awakening from REM sleep and ketamine anesthesia. *Purple traces* indicate VS patients who show high-complexity EEG responses to nTMS despite being behaviorally unresponsive. A *white cross* on the cortical map indicates the stimulation target of nTMS

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Brain Plasticity in Neurosurgery

16

Petro Julkunen and Jari Karhu

16.1 Brain Plasticity: Unmasking Existing Connections and/or Establishing New Ones

Plasticity is currently taken as an intrinsic property of the human nervous system and does not necessarily represent behavioral gain. Network plasticity is the mechanism for development and learning, as well as a cause of maladaptive reorganization such as epileptic phenomena in conjunction with brain tumors.

The human CNS is capable of change and adaptation (both short and long term) throughout life (for reviews, see Kaas 1997; Pascual-Leone et al. 2005). Unmasking of existing connections, shifting synaptic weighting, and even sprouting of new dendritic connections and formation of new synapses are possible (Kaas 1997). These modifications can be driven by afferent input, which is often inseparable from efferent demands and the functional significance of tasks. Despite the largely uncertain exact molecular and biophysical determinants, enough repetitions of a given task or stimulus in the human neuronal system is likely to give rise to long-standing modifications in participating networks. Plastic changes seem to underlay the acquisition of new skills, the adaptation to new contexts, and the recovery of function

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after injury. The other issue regarding motor output maps is the question of what is represented in the motor cortex: muscles, postures, or movements.

Brain plasticity in adults can be observed, for example, via fast induction in stroke (Rossini et al. 2003). Indications of brain plasticity in slow-growing lesions provide theoretical support for enabling surgery in areas essential to language or motor function that might otherwise be considered inoperable (Duffau 2005; Desmurget et al. 2007). Gray matter plasticity is accompanied by white matter plasticity of subcortical pathways affecting reorganization (Szalisznyo et al. 2013). Hence, major tumor resections without induction of functional loss in networks with preserved connectivity and good prognosis after stroke lesions with preserved motor tract functional connectivity both exist and demonstrate the different modes of plasticity, while it may be that the plasticity of white matter is more limited than that of gray matter (Ius et al. 2011; Di Pino et al. 2014). Consequently, brain plasticity may allow there to be no neurological symptoms even when large tumors are present. Comparison of the recovery for slow-growing lesions and that of acute injuries has suggested different reorganization patterns (Desmurget et al. 2007; Keidel et al. 2010). For recovery, a concept of "minimal common brain" has been introduced, which suggests that there exists a set of mechanisms or networks that is necessary for basic cognitive functions so minimalistic that it is not sufficient for complex functions (Ius et al. 2011).

Brain plasticity is commonly considered to cover adaptive changes in neural networks including cellular, synaptic, and pathway changes, which exhibit as functional reorganization (Smits et al. 2015). In this chapter, we extend the definition to include those changes that have the appearance of plasticity but are potentially caused by mechanical effects.

16.1.1 Single-Cell Level Plasticity (Intrinsic Excitability)

At the single-cell level, synaptic plasticity refers to changes in the connections between neurons, whereas nonsynaptic plasticity refers to changes in their intrinsic excitability. In general, the connections between network components are prone to synaptic plasticity, while component functions themselves (i.e., intrinsic excitability) of the neurons are prone to intrinsic plasticity.

Intrinsic excitability is the net sum of excitatory-inhibitory single-cell reactions to either synaptic input (Koch 1998) or exposure to external whole-cell stimulation such as an electric field induced by TMS (Muller-Dahlhaus and Vlachos 2013). It may be attributed mostly to the balance and distribution of fast- and slow-adapting ion channels leading to adaptive changes in membrane excitability and conductance. When a neuron is stimulated by an external electric field, the geometry of the dendrites and axons in the stimulating field also has a profound effect on the overall excitability of a single neuron. Indeed, the same principle can be expanded to glial cells and to all cells in the brain with sufficient length of neuronal projections in relation to field strength (Ruohonen and Karhu 2010).

16.1.2 Synaptic Plasticity

The connections between neural network components with anatomical proximity and/or connections to, for example, injured or lesioned cortex are prone to synaptic plasticity, which is required for learning (and memory). This is the prerequisite for neuronal adaptation to injury or lesion and subsequent restoration of functions. For example, Koch coined and elucidated a terminology for "synaptic strength" (Koch 1998). The coupling strength of two neurons is described in terms of n = the number of presynaptic transmitter release sites, p = the probability of transmitter release, and q = some measure of postsynaptic response such as current, voltage, or conductance change. Taken together, these measures can be used to determine the time-dependent response $R = npq$ for "quantal" handling of the synaptic efficacy in neural networks, providing a simplified method for the characterization of plastic network changes.

16.1.3 Hebbian Plasticity

Hebb described plasticity using the example of two adjacent neurons that could take part in firing each other with the efficiency of the firing cells increased as a consequence of some growth process or metabolic change (Hebb 1949). The original formulation is nowadays often described as "what fires together, wires together." Nevertheless, Hebb's principle fits nicely together with the quantal description of synaptic plasticity. Moreover, it fulfills the basic empirical requirements for LTP, which is the best known and most studied neuronal learning—and adaptive—mechanism in the mammalian brain.

The healthy human brain is known to display adaptation plasticity. Learning new skills results in the adaption of the neural networks involved in the developed or trained function (Adkins et al. 2006; Muellbacher et al. 2001; Pascual-Leone et al. 1995). This type of Hebbian adaptation has been observed in different types of groups, such as musicians and athletes (Rosenkranz et al. 2007; Elbert et al. 1995; Pearce et al. 2000; Vaalto et al. 2013; Tyc et al. 2005). Musicians are a good model of use-dependent adaptation neuroplasticity with, for example, adaptive changes in Broca's area (Sluming et al. 2002; Abdul-Kareem et al. 2011) and M1 (Bangert and Schlaug 2006; Vaalto et al. 2013). These types of adaptive changes in the brain may continue and become active when required (e.g., to enhance or restore brain functions). To understand the analogy behind adaptive neuroplasticity, neural network models may be used.

16.1.4 Modulation of a Neural Network

The plastic effects of lesions and surgery can be understood using the principal concept of neural networks. The cortical neural networks are organized and communicate in such a way that multiple parts of the network have either excitatory or

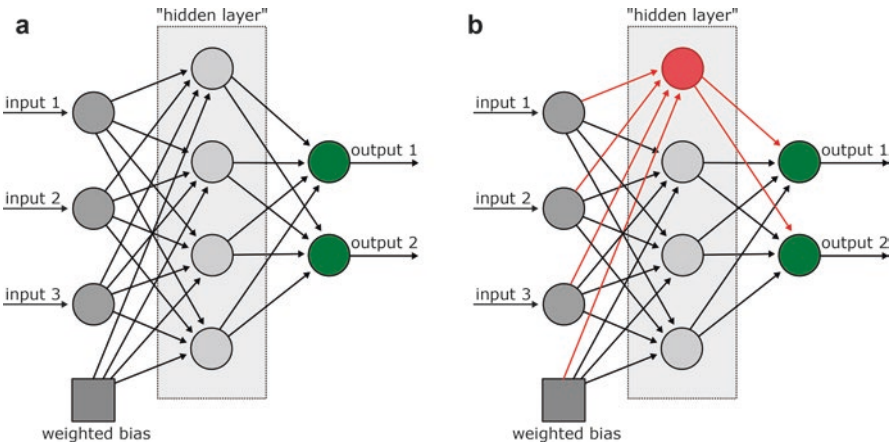

Fig. 16.1 Neural network example of normally functioning (**a**) and lesioned network (**b**) and resulting modulation of network function adapting to impairment in parts of the network. The neural network represents a simplistic view of a functional network of neurons in the brain, which has an input and an output. The inputs are modulated by a hidden layer of excitatory and inhibitory neurons to produce a certain output (*green circles*). If a lesion (e.g., tumor or stroke) impairs an input or part of the network (*red*), the output is affected and requires adaptation from the network to compensate for the impairment. A weighted bias from outside the network may control for the weight of the effect of each component in the network via, for instance, modulation of the general level of excitation or parallel/connected networks

inhibitory effects on the input impulses to produce the output of the network (Fig. 16.1). These components have been optimized through learning and adaptation to produce and control common brain functions. In other terms, the convergence of neural input processing yields an output observed as executed neural function. A suitable neural function is the objective function that is produced by a neural network with energy-efficient minimum network size, noise, and error (Laughlin and Sejnowski 2003). For instance, in the sensorimotor system, the input of the neural network could be an external stimulus-induced evoked response in the brain, which activates the "hidden layer" of the neural network to modulate and process the response and to produce an output, potentially the onset of a type of motor action. Depending on the input, the hidden layer of the network modulates the neural impulse to produce an output, and hence the output depends on the inputs of the neural network and the modulatory and controlling effects of the hidden layer (Fig. 16.1a).

If the inputs are not producing a wanted or suitable output, the hidden layer may adapt. Also, if the hidden layer or the inputs are impaired as part of the neural network, the output will discontinue to produce a suitable response, and adaptation of the remaining hidden layer is required to minimize errors in the objective function or output (Fig. 16.1b). The Hebbian theory (Hebb 1949) describes a mechanism of synaptic plasticity, which in the neural network context affects the connections

between the components (e.g., nodes, neurons, or local networks of neurons) in the network. New connections or modified connections between components may be formed in order to compensate for the impaired network and/or input. The biasing of the different components affecting the output could be adjusted at the general level via modulation of excitation levels. In addition, new connections to other existing neural networks could be formed. The number of impaired connections and the location of the impairments within the network determine the type and extent of adaptation required. Hebbian plasticity is required for forming new connections, while intrinsic plasticity is required for regulation of synaptic plasticity, to which the component functions (i.e., intrinsic excitability) of the neurons are prone. These two, together with the weighted bias of the different components from outside the network, form the mechanism through which adaptation to lesion- or injury-induced impairment of neural networks can occur.

The true neuronal functions could have several layers (i.e., several hidden network levels) deriving from the outputs in Fig. 16.1. As such, impaired parts of the neural networks likely have effects that cascade into multiple outputs of several layers of the neural functions. On the other hand, there will be a greater number of compensating network components, and, hence, a lower level of adaptation from the individual components may be required than in a small network. The plasticity required for a brain function recovery after focal lesion or injury therefore involves the areas in the vicinity of the lesion and requires the reorganization of all brain networks (Szalisznyo et al. 2013; Guggisberg et al. 2008). To understand the analogy of multiple layers and connections, neurons are suggested to be able to receive and deliver signals via thousands of synapses, thereby extensively processing inputs to implement all information operations in the nervous system (Laughlin and Sejnowski 2003). Consequently, resectable areas of the brain should be considered as components within the neural network, meaning that, after their removal, the neural network should reorganize to eventually preserve behavioral function (Ius et al. 2011).

In an ideal case, neuronal networks provide energy-efficient, spatially compact, and accurate processing of the input signals to generate suitable outputs for brain functions (Laughlin and Sejnowski 2003). However, the true weighting of these different, sometimes competing, objectives for outputs is unknown and complex, indicating that the convergence of neural networks adaption is as continuous as are the changes in inputs and objectives for optimal outputs. The recently coined term "metaplasticity" suggests that modification of the direction, magnitude, and/or duration of plasticity is defined by previous activity in the same postsynaptic neuron or neural network. Thus, any given synapse would be bidirectional (i.e., either LTP or LTD can be induced), and the probability of this induction is not stable over time. However, this depends on the activity of the postsynaptic neuron, which would be highly relevant for any neuromodulatory attempt to "drive" adaptive plasticity.

The application of cost functions to understand differences between types of recovery through reorganization of the neural networks has revealed realistic differences between slow-growing lesions and acute injuries (Keidel et al. 2010). The

intrinsic properties of the components within the neural networks may also be affected by maladaptive plasticity. In epilepsy, the components within the network activate synchronously with adjusted firing rates to cause changes in overall network function and excitability.

The neural network components and connections, and their modification through injury, lesion, or adaptation in the neural network, determine the potential for reorganization of the network. Considering the brain areas in the proximity of a resection as components in a neural network will aid in understanding the reorganization required in order to preserve function after their removal. To minimize the extent of required reorganization within the network, connectivity should be protected.

16.2 Imaging Plasticity with nTMS

Multiple modes of neuroimaging enable imaging of brain plasticity effects, and the interaction between lesions and functional cortical areas can be revealed. Commonly, the relative localization of the functionally relevant cortical sites is done presurgically to determine surgical constraints and to aid in planning the procedure. Targeting a functionally active locus on the cortex using nTMS may produce a measurable response. Since the motor systems of the brain are more responsive in terms of induced response interpretation than the sensory systems of the brain, the produced responses can be recorded time locked to the stimulus and its location. Suitable responses are typically motor responses recorded from muscles using EMG or interruption responses in language performance recorded using real-time video recording. While it is likely possible to identify plasticity effects in the language-related brain areas, the main focus has been in the motor areas with muscle responses, as quantification of the induced responses is convenient when using stimulation-triggered EMG in evoked responses like MEP or CSP (Pitkänen et al. 2015; Jussen et al. 2016; Vaalto et al. 2013; Foltys et al. 2003; Forster et al. 2012; Mäkelä et al. 2013; Säisänen et al. 2010; Pascual-Leone et al. 1994).

A cortical map can be constructed of stimulus locations accompanied by response size (Julkunen 2014; Kallioniemi and Julkunen 2016; Pitkänen et al. 2015; Forster et al. 2012) (Fig. 16.2). The produced cortical map is fixed to the time of the mapping. Therefore, the plasticity-induced effect before or after the mapping cannot be quantified without separate mapping data. For neurosurgery, the most important application of nTMS is to produce momentary cortical maps representative of certain neural functions. These cortical maps are alternatives to cortical maps produced by other methods such as fMRI, PET, single-photon emission computed tomography (SPECT), EEG, or DES. These methods may complement and contradict each other. As neuroplasticity arises in several ways, it appears in different cortical maps in different ways. The accuracy of these methods is limited due to local neurovascular and metabolic coupling, physical properties of the tissue, and the fact that distinguishing essential areas from modulatory areas—that is, areas that need to be preserved and areas that can be resected without permanent harm—cannot be made with confidence (Ius et al. 2011).

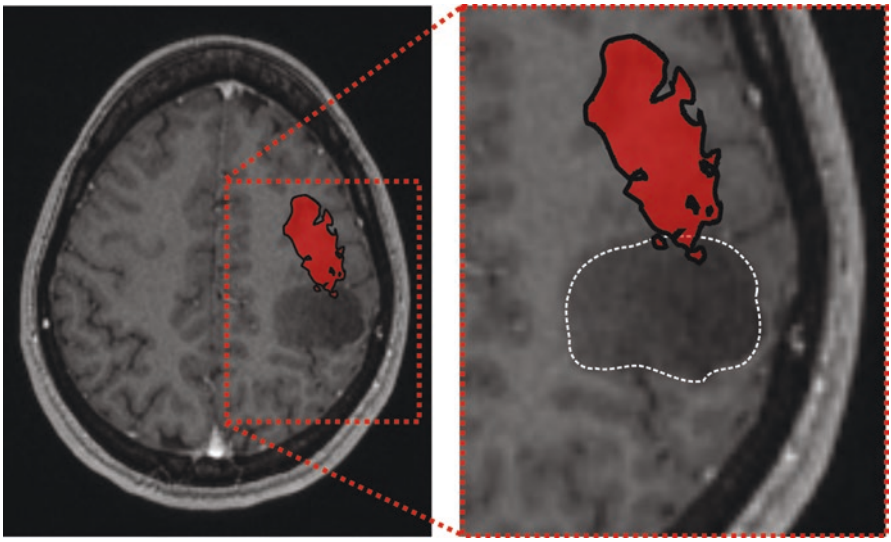

Fig. 16.2 Example of an outlined cortical map of hand muscle function on the M1 overlaid on an axial MRI slice. The functional area is represented as *red*, and the tumor and affected anatomical structure is outlined with a *white dashed line* in the close-up on the right. Outlining was performed using spline interpolation of MEP amplitudes (Julkunen 2014)

16.2.1 nTMS Cortical Maps for Detecting and Accounting for Plasticity

The nTMS technique is used to construct cortical maps as a clinical procedure, for example, preceding surgery or radiotherapy (Conti et al. 2013; Kato et al. 2014; Säisänen et al. 2010; Lefaucheur and Picht 2016; Picht et al. 2009). To observe plasticity effects in cortical maps, parameters measured from the maps are used for quantitative evaluation: center of gravity (COG), map area, MEP volume, number of responses, rMT, and MEP amplitude. *COG* represents a spatial average of the cortical map of a function (Julkunen 2014; Kallioniemi et al. 2016; Borghetti et al. 2008; Byrnes et al. 1998; Classen et al. 1998; Freund et al. 2011; Wassermann et al. 1992) and can be used to detect shifts or relocation (Byrnes et al. 1998; Siebner and Rothwell 2003). *Map area* can be estimated based on response-size distribution to compute streamline edges for the cortical map to evaluate the size of the function's cortical area (Julkunen 2014; Pitkänen et al. 2015; Jussen et al. 2016). The cortical map has also been evaluated using *MEP volume* maps by summing up all responses (Hetu et al. 2011; Kesar et al. 2012) or by counting number of induced responses/active sites on a stimulus grid (Gagne et al. 2011; Foltys et al. 2003; Malcolm et al. 2006; Pascual-Leone et al. 1995). To study excitability changes, simple measures of response threshold or response amplitude can be conducted (Pascual-Leone et al. 1995).

16.2.2 Physical Changes in Cortex Affecting Brain Mapping with nTMS

From a physical perspective, plasticity effects can be expected to be visually apparent during presurgical mapping of functional cortical areas, as plasticity preceding cortical mapping procedure may have reorganized the network by altering (1) the location of functional motor areas (*relocation*), (2) the extent of the functional motor areas (*resizing*), or (3) the excitability of the functional motor areas (*excitability*). Surgical operation may also either directly or indirectly facilitate plasticity to arise in similar ways. Therefore, the types and underlying reasons for plasticity effects may need to be identified.

The known physical factors and most important determinants that affect nTMS mapping of the cortex include the distance from TMS coil to the cortical surface, TMS coil placement (position, rotation, tilt), the induced electric field direction with respect to the cortical neuronal organization, the neuronal organization and the strength of the stimulus, and stimulus characteristics (Schmidt et al. 2015; Danner et al. 2012; Julkunen et al. 2012; Kallioniemi et al. 2015; Ruohonen and Karhu 2010). These physical factors provide the underlying theory for how changes that have the appearance of plasticity are revealed with nTMS mapping. However, these factors do not account for the neuronal plasticity effect causing reorganization of the cortical functions. Instead, macroscopic lesions close to the stimulated area, such as tumors, cause physical effects that may exhibit as change in location, size, and excitability.

For instance, a tumor located in the vicinity of M1 could, as a result of expansion, cause dislocation of the cortical structure, giving the appearance of relocation plasticity. An extracortically located tumor that is dislocating the cortex could increase the distance between the stimulated cortex and the coil, which would necessitate greater stimulation power to achieve sufficient excitation in the cortex (Fig. 16.3c). This could give the impression of reduced excitability and/or a wider area of cortical excitation in the immediately adjacent tissue. Alternatively, a subcortical tumor that is compressing the cortex from beneath could push the cortical surface from inside the sulcus toward the stimulation coil, hence reducing the stimulation power required to achieve cortical excitation and response (Fig. 16.3b and d). This could lead to an impression of increased excitability. Compression and stretching of the cortical tissue will likely be observed as changed excitability as well, as the neuronal organization is affected and therefore the excitable volume of neurons upon stimulation is altered, including a different volume of activated neurons.

Compression and stretching could further give the impression of resized functional areas. Changes in the curvature of the cortex may also affect apparent excitability and hence affect the required stimulation power. Dislocation of a functional area may therefore be accompanied by changes in excitability. Similar types of changes may occur in the axonal pathways (Fig. 16.4).

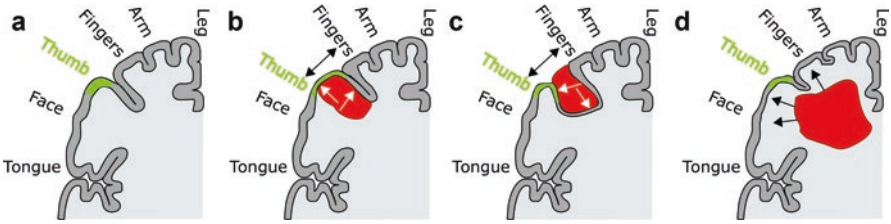

Fig. 16.3 Effect of lesion growth within M1 represented in simplified schematic images. In the images, a coronal view is used for 2D visualization of the common homunculus for simplicity reasons. (**a**) Normal, intact brain in adult human subjects. Functional area of the thumb is highlighted in *green*. (**b**) A subcortical growth affecting cortical tissue geometry and causing mechanical dislocation of the muscle representation area by compression of the cortex from beneath. (**c**) An extracortical growth affecting tissue geometry and causing mechanical dislocation of the muscle representation by compression of the cortex from the outside. (**d**) A large subcortical growth causing subcortical tissue dislocation and resulting compression of the cortical structure. Vectors in the images indicate the direction of compression. Lesions are represented as *red areas*

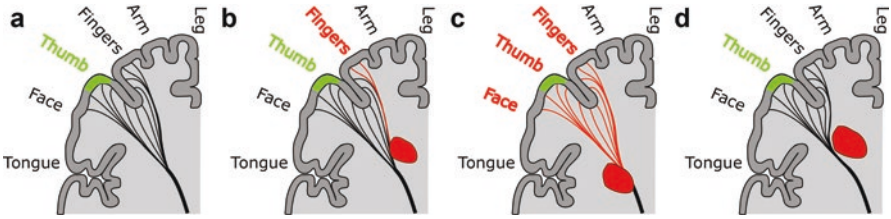

Fig. 16.4 Effect of lesion growth within the axonal motor pathway represented in simplified schematic images. In the images, a coronal view is used for 2D visualization of the common homunculus for simplicity reasons. (**a**) Normal, intact brain in adult human subjects. Functional area of the thumb is highlighted in *green* with connected descending axonal pathways as *black lines*. (**b**) A subcortical lesion affecting parts of the descending motor pathway and partly impairing connectivity and motor function. *Red lines* indicate the affected axonal pathways. (**c**) A subcortical lesion affecting a large portion of descending motor pathway and impairing connectivity and motor function. (**d**) A subcortical lesion affecting parts of the descending motor pathway by compression and dislocating the motor pathway with potential effects on motor function and connectivity. Lesions are represented as *red areas*

16.3 Plasticity Effects in nTMS Cortical Maps Directly Relevant to Neurosurgical Procedures

16.3.1 Plasticity Preceding Surgery

Plasticity preceding surgery may occur in various ways, some of which may be important to identify prior to surgery. For this reason, analysis of brain anatomy may not be sufficient and functional analysis may be required. To account for

plasticity-induced changes in normal brain function and anatomic brain areas, plasticity preceding surgery must be mapped. Here we consider the sources of plasticity in three types: lesion-induced, use-dependent, and maladaptive plasticity. *Lesion-induced* plasticity may be caused e.g., by stroke or tumor, while *use-dependent* plasticity may be e.g., due to muscle disuse, amputation, or training (Elbert and Rockstroh 2004). *Maladaptive plasticity* may be e.g., due to focal cortical dysplasia (FCD) causing epilepsy or to adaptation to neural network changes causing pain or tinnitus (Langguth et al. 2005). The separation of the types is not strict and they may overlap, as they do in the case of FCD, which can induce lesion-induced and maladaptive-type changes. FCD has been demonstrated to cause a major reorganization of motor function (Narayana et al. 2015) (Fig. 16.5a and b). In addition, large lesions or injuries could have radical effects on the reorganization of cortical functions. Radical cortical reorganization has been demonstrated after partial hemispherectomy to treat refractory seizure disorders (Narayana et al. 2015) (Fig. 16.5c). The appearance of plasticity in this way is likely affected both by the dysfunctional hemisphere and the partial hemispherectomy.

Brain plasticity in the context of neurosurgery does not need to be adaptive plasticity; the appearance of plasticity may simply be due to mechanical pressure from a lesion causing changes in function and altered appearance in cortical maps (Conway et al. 2016). Once the source of mechanical load (e.g., tumor) is removed, normal function may be regained with no plastic adaptation required. Therefore, unlike use-dependent and maladaptive plasticity, lesion-induced plasticity is not necessarily associated with adaptation. Use-dependent plasticity manifests due to changes in activation of the cortex and the peripheral connections. It is easily demonstrated via immobilization of restrictions of movement or related muscle disuse, which may reduce the size of the functional motor area in a cortical map (Liepert et al. 1995; Elbert and Rockstroh 2004), while training of skills may expand the functional motor area (Elbert et al. 1995; Pascual-Leone et al. 1995; Vaalto et al. 2013; Elbert and Rockstroh 2004). Also, learning a fine motor skill may confine the motor function (Vaalto et al. 2013).

Maladaptive plasticity exhibits as harmful adaptation to neural network changes, such as in FCD, which may cause epilepsy or pain by disturbing normal neural network function. The different sources of plasticity may interact to produce the final summation of the plasticity effect that is observed in the cortical map. Interacting multiple effects of plasticity may complicate the identification of different sources of plasticity based purely on the cortical map; however, a structural MRI may help by imaging the axonal pathways using DTI with tractography (please see Chap. 6). Lesion-induced impairment of normal function has been shown in cortical and subcortical structures and pathways (Papagno et al. 2011). Likely, effects of lesion-induced plasticity are the relocating and resizing of the functional areas. A subcortical efferent lesion may cease a descending motor tract from functioning at different locations of the tract, whereas altered sensory pathways may change functional activation patterns feeding into motor functions and therefore induce plastic effects.

Previously recorded plasticity effects due to lesions in the brain are numerous; the most fundamental of these are stroke and tumors. Gliomas have been shown to

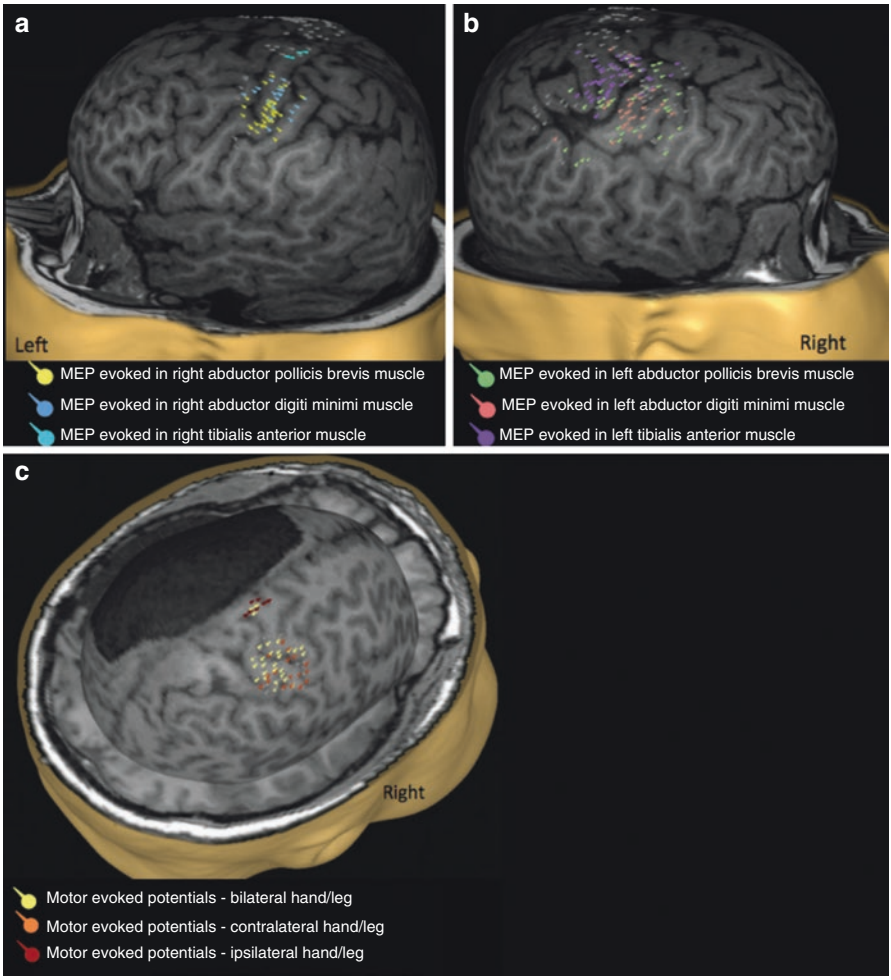

Fig. 16.5 Functional reorganization of the motor cortex. (**a**) nTMS motor mapping demonstrating the effect of cortical dysplasia on cortical functional reorganization in a 13-year-old girl. Normal organization of the left motor cortex with normal cortical localization of the right hand and leg. (**b**) Polymicrogyria and the vertical cleft extending from the posterior aspect of the right Sylvian fissure. The location and extent of the left-hand muscle representation in the right hemisphere is aberrant and localized over the area of polymicrogyria with the displaced location of the primary leg motor cortex. (**c**) nTMS motor mapping demonstrating cortical reorganization in a 16-year-old female patient who had suffered left hemisphere trauma at 32 weeks' gestation. Bilateral limb representation is noted in the right primary hand and leg motor area. (Modified from Narayana et al. 2015 with permission)

cause relocation of the functional motor areas, as they tend to shift motor areas in their close vicinity (Takahashi et al. 2012; Conway et al. 2016). Similar observations have been made in language-related areas as a potential hemispheric shift (Krieg et al. 2013; Rösler et al. 2014). In addition, SMA appears to play a major role in motor cortex plasticity in HGG patients (Majos et al. 2015). Cortical maps of

LGG patients have revealed various patterns of reorganization with brain functions remaining within the tumor, reorganizing around the tumor, spreading in the ipsilateral hemisphere, or even moving to the contralateral hemisphere (Desmurget et al. 2007). Cerebral palsy has been shown to relocate motor function by enabling ipsilateral activation of the primary motor tract with nTMS (Pihko et al. 2014). In epilepsy, the epileptogenic zone can often be detected with an MRI as reorganized structures. Evaluation of the epileptogenic zone can be done using a variety of functional imaging techniques combined with anatomic imaging. The use of cortical TMS mapping has demonstrated the representational adaptations of the motor cortex in epilepsy, when epileptogenic focus involves a motor area (Labyt et al. 2007). The adaptations include changes in excitability and apparent representation resizing, potentially due to modified inhibition and representation shift. FCDs, a common cause of intractable epilepsy, are known to reorganize the local network (Sisodiya et al. 2009; Otsubo et al. 2005). Intracranial AVMs are also known to induce plasticity, the effects of which can be observed using nTMS (Kato et al. 2014). Previously, right-sided language lateralization in AVM patients has been reported (Lehericy et al. 2002; Pouratian and Bookheimer 2010; Vikingstad et al. 2000).

In stroke, the timing of creating the cortical map is crucial, as vast time-dependent changes tend to occur both in the acute and subacute phases, while milder changes may still occur during the chronic phase (Julkunen et al. 2016a, b; Mäkelä et al. 2015). Stroke-induced plastic changes may reveal extensive plasticity effects (Fig. 16.6). Unlike stroke, where plastic effects are rehabilitative and potentially recovering toward normal function, tumors and lesions tend to exhibit a progression

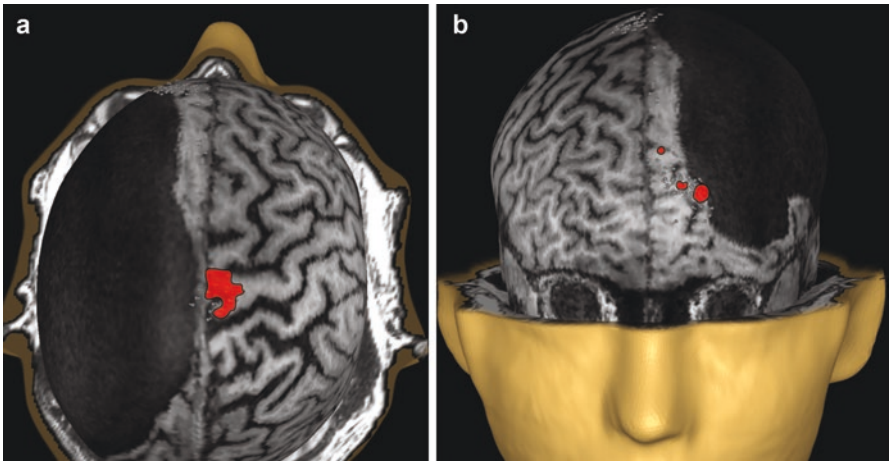

Fig. 16.6 Functional reorganization after stroke. (**a**) Left-foot and (**b**) right-foot muscle representation revealed by nTMS mapping in a 19-year-old male epilepsy patient with right-sided hemiparesis and an extensive perinatal vascular infarction in the left middle cerebral artery territory. Sites eliciting MEPs are indicated by *red color*. Image data by courtesy of Jyrki Mäkelä (Mäkelä et al. 2015)

that steers brain function away from normal function, and adaptive and nonadaptive processes may induce plasticity to occur in various ways, such as relocated functional area, extended functional area, and altered excitability (Conway et al. 2016; Krieg et al. 2013). With nTMS, relocation of motor areas may also be disguised as altered excitability when a tumor of subcortical origin extends/pushes the cortex toward the skull, thus reducing coil-to-cortex distance and giving the appearance of a lower excitability threshold and diminished functional map due to suboptimal stimulus strength.

For neurosurgical applications of cortical mapping and to understand/account for plasticity effects, it may be of interest to determine whether the observed plastic changes prior to presurgical mapping are expected to continue after surgery and therefore potentially affect long-term brain function.

16.3.2 Plasticity Following Surgery

Normalization of the plastic effects preceding surgery may occur after surgery. However, relocation after surgery may predominantly be observed as a shift toward the resection cavity as has been reported in the case of gliomas (Conway et al. 2016). Potentially, this shift or lesion-induced relocation prior to surgery may not have induced adaptive changes, and removal of the source of mechanical tissue compression may allow for a quick recovery. The vascularization of the cortex close to the resection cavity also plays a critical role. A report on extra-intracranial bypass surgery in occlusive cerebrovascular disease suggests a reversibly impaired cortical motor function in the ischemic brain with cerebral revascularization leading to improved motor output, observed as increased cortical motor excitability and resized motor representation (Jussen et al. 2016).

The reversible effects of the plasticity preceding surgery may occur as the original inductor is removed. In the case of lesion-induced plasticity preceding surgery, the lesion removal may, in addition to the aforementioned relocation, allow for retaining neural network connections, enabling adaption to normal network function. This is expected after tumor resection in the form of normalized excitability, functional recruitment, and most of all normalized brain function. For instance, in the case of retained muscle function, use-dependent plasticity may cause recovery of the motor representation to be observed in the cortical maps (Fig. 16.7). Similar effects can be observed with language function. Obviously, the mechanical effect of the resection cavity needs to be accounted for (Conway et al. 2016).

As maladaptive plasticity may be caused by changes in the input to the neural network, the brain may try to compensate for lower-level input by increasing the excitability level of the remaining neural network (see weighted bias in Fig. 16.1), which could cause false outputs in the network to appear as unwanted functionality of the neural networks. This type of maladaptive plasticity could be caused by surgical procedures and perhaps appear as delayed effects after surgery. These may be caused by both resection itself and vascular changes.

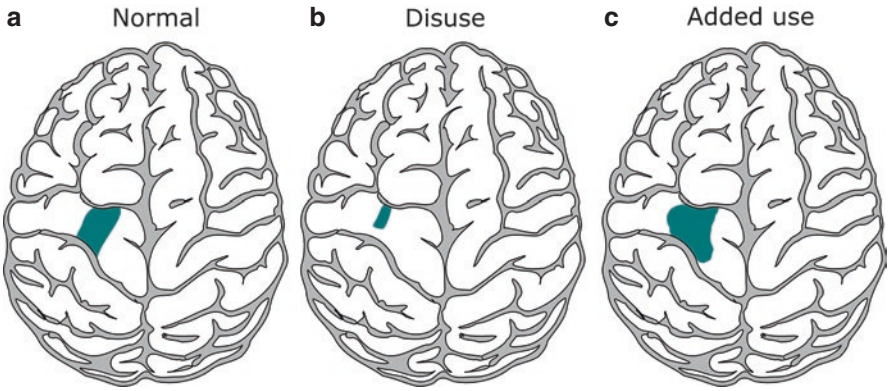

Fig. 16.7 Use-dependent plasticity. Schematic example of potential effects of use-dependent plasticity on functional hand motor area of the M1. (**a**) Normal representation area (as *green*). (**b**) Effects of long-term disuse of the muscle result in reduction of size of the functional motor area (Liepert et al. 1995; Elbert and Rockstroh 2004). (**c**) Added use via training may expand the functional representation area (Elbert et al. 1995; Pascual-Leone et al. 1995; Elbert and Rockstroh 2004)

16.4 Final Discussions on Plasticity Effects in Cortical Maps

Even though the effects of different types of plasticity may be observed as a summation in the cortical nTMS map, it may be impossible to identify the different sources of plasticity due to various chemical and mechanical factors causing the observed plasticity effects. While some of the plasticity effects may be relevant to identify for the cortical map construction for neurosurgical applications, some effects of plasticity are irrelevant for the time scale used for preoperative mapping, currently the most important application of nTMS in neurosurgery. Short-term plasticity is usually controlled and considered negligible for the mapping procedure, as time between mapping and surgery/radiotherapy is commonly short and should be kept short; this is especially true in cases where quickly occurring plastic changes are expected (e.g., in aggressive tumor growth). Theoretically, an aggressive tumor growth affecting either the cortex or the subcortical tracts could cause some of the plasticity effects to occur between the mapping and surgery, and therefore the validity of the mapping could be compromised.

As the indications for neurosurgical operations vary and functional reorganization might show potentially rapid (transient) effects (Duffau 2006), localizing the brain functions and connected tracts needs to be performed individually. Even though there are functional limitations in each imaging technique, combinations of different methods will lead to the best results in terms of surgical indications and optimal EOR (Ius et al. 2011). The combination of DTI with nTMS enables assessment of cortical function and connected white matter tracts (Negwer et al. 2016; Conti et al. 2014; Frey et al. 2012) (Chaps. 6 and 9). This can also be achieved by combining DTI and fMRI, albeit the determination of the cortical "seed" or origin of the tracts is arguably more inaccurate (Kamada et al. 2007).

Brain plasticity is often considered to be the normal ongoing state of the CNS throughout life (Pascual-Leone et al. 2005). However, the state and demand of plasticity is modulated heavily by lesions, injury, or surgical interventions affecting the neural networks of the brain. The emphasis on the continuous ongoing state of plasticity is crucial with slow-growing tumors that necessitate continuous functional reorganization and implementation of compensatory networks (Desmurget et al. 2007; Ius et al. 2011). In addition, areas outside the damaged area may take over the impaired functions while facilitating recovery (Duffau 2006). The dynamics of the reorganization of brain networks occurring through adaptation in everyday life or after a lesion demonstrate the versatile redundancies that exist in the brain available for functional substitution (Ius et al. 2011; Bavelier and Neville 2002; Duffau et al. 2000; Schieber and Hibbard 1993; Rossini et al. 2003). Understanding the plasticity of functional brain areas is important for optimizing individual surgical options.

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Outlook on the Potential of nTMS in Neurosurgery

17

Phiroz E. Tarapore and Mitchel S. Berger

17.1 Introduction

In many specialized neuro-oncological centers worldwide, the integration of nTMS into the preoperative clinical workflow occurred quite quickly. In so doing, neurosurgeons and neurophysiologists had to learn how to use this new data optimally. This book has sought to describe those learned lessons in detail.

The purpose of this final chapter is, however, to anticipate and motivate the next generation of nTMS applications over the next several years. While we already have clinical data in support of current diagnostic applications (preoperative mapping of motor and language function), nTMS has the potential to develop in two additional ways: (1) preoperative mapping of further brain functions (Chap. 11) and (2) tailoring treatment decisions based on the longitudinal assessment of tumor-induced functional reorganization, as conducted with nTMS follow-up studies.

Besides this diagnostic direction, nrTMS will also be used therapeutically to induce functional reorganization. The treatment protocols for postoperative acquired deficits will likely be similar to those applied poststroke. However, the induction of functional reorganization, so-called prehabilitation, so as to make highly eloquent tumors safer for resection, is a completely new field. Before this application is ready for clinical use, we must answer several proximal research questions.

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17.2 Diagnostic Use for Detecting Functional Reorganization

17.2.1 Current Knowledge on Lesion-Induced Functional Reorganization

There is increasing evidence that intraparenchymal brain tumors promote functional reorganization, which means the relocation of cortical function from one brain region to another (Duffau 2006; Ius et al. 2011; Krieg et al. 2013c; Kawashima et al. 2013; Southwell et al. 2015). Particularly in the case of slow-growing tumors, cortical function does not reside in the typical, anatomically defined brain region. These brains are different from those of healthy people, because the tumor itself induces reorganization of cortical function to other brain areas (please also see Chap. 16). In 2008, Duffau and colleagues reported how they were not able to resect gliomas completely during the first surgery because intraoperative mapping by DES showed eloquent motor or language function within the region of the tumor (Robles et al. 2008). They followed these patients postoperatively, waiting for functional reorganization to take place. On repeat surgery, they were able to resect the tumor residual, because DES showed no further function in the tumor area. Our group also observed functional reorganization when examining 18 patients who underwent repeated awake surgery with intraoperative DES mapping. We found a loss of function in previously motor- or language-positive brain areas in 6 out of these 18 patients and a gain of function in another patient who showed new essential motor and language function in previously negative areas (Southwell et al. 2015).

While this capability is profoundly exciting, it is important to distinguish between cortical and subcortical functional reorganization. Injury to the cortex can potentially recover; subcortical white matter lesions, on the other hand, are often irreversible (Herbet et al. 2016). Stroke patients, for instance, potentially change the organization of their motor cortex within 6 months after the ischemic event leading to improved motor function (Chap. 14) (Freundlieb et al. 2015). Glioma patients, in particular, can preserve motor abilities despite tumor infiltration within their M1 as described above (Duffau et al. 2002; Duffau 2005; Robles et al. 2008).

The potential for functional reorganization is not equal in all cortical regions. Primary unimodal cortex, such as the precentral gyrus, is less capable of reorganization than higher-order cortical regions such as the left angular gyrus or dorsal superior temporal gyrus. One reason for this difference may be that cortices with a distinct function, such as the precentral gyrus or Wernicke's area, have a critical role within their functional network; thus, the capacity for functional reorganization is limited—and the absence of functional reorganization implies severe deficits. In contrast, other brain regions with less distinct functional determination participate in wider cortical networks, and compensation for their role is easier if they become infiltrated with tumor. Some areas represent an intermediate level of functional integration, such as supplemental areas responsible for the fine-tuning and coordination of functional processing. Two such regions are the SMA of the SFG (motor function) or the left-sided MFG and IFG (language function).

In contrast to cortical regions, the impairment of subcortical tracts usually results in severe functional impairment without significant capacity for functional recovery

(Galluzzi et al. 2008). This finding applies to glioma patients as well as stroke patients—subcortical tracts are far less likely to show functional reorganization if infiltrated by a tumor (Herbet et al. 2016).

Because language is organized as a complex and adaptive network, including multiple subcortical pathways connecting the same cortical areas, language function is more likely to exhibit functional reorganization than motor function (Duffau 2014b, 2005; Ius et al. 2011; De Witt Hamer et al. 2013; Herbet et al. 2016). There are various theories on the mechanisms of cortical neuroplasticity. The two most accepted theories are addressed here (please also see Chap. 16). In the first theory, adjacent neurons in the corresponding cortical layer are recruited, as has been shown for traumatic brain and spinal cord injury patients (Harris et al. 2013; Di Rienzo et al. 2014). Such recruitment can also occur via existing contralateral connections (Levy et al. 2008). The second theory involves the disinhibition of inhibitory interneurons (Duffau 2014a). Functional synapses are eliminated during development because they represent redundant connections ("synaptic pruning") (Schuldiner and Yaron 2015). In the setting of injury, during which some of these primary connections are disrupted, previously inhibited redundant circuits are recruited in order to improve the impaired function. Thus, injury or functional impairment can promote the reactivation of these latent compensatory tracts (Gaucher et al. 2013; Duffau 2001).

While recruitment takes considerable time to develop, the unmasking of latent redundant circuits can occur immediately. Concerning glioma patients, there is evidence for both mechanisms. Short-term functional reorganization has been shown in the precentral gyrus intraoperatively within the ipsilateral cortex, while recruitment of the contralateral SMA was shown to develop during long-term follow-up and corresponds with improved functional recovery after SMA resection (Duffau 2001; Krainik et al. 2004). Similar ipsi- and contralateral functional reorganization has also been reported for language function (Sarubbo et al. 2012; Krieg et al. 2013c, 2014). Despite the relative paucity of data on functional reorganization, some factors affecting functional reorganization have been identified. These factors include age, growth kinetics of the lesion, tumor location, affected function (network vs. unimodal), and gender (Galluzzi et al. 2008; Keidel et al. 2010; Charras et al. 2015; Kuo et al. 2006). Although data showing the high potential of functional reorganization for neurosurgical patients is growing, functional reorganization cannot be relied upon to restore function after surgery—preservation of function is far preferable to restoration of function, and the best outcomes require safe surgery that includes intraoperative DES mapping.

Following functional reorganization with nTMS opens a new horizon in neuro-oncology, since a tumor in a presumed eloquent location, be it in motor cortex, language cortex, or subcortical structures, may still be considered safe for surgical removal (Takahashi et al. 2012; Kawashima et al. 2013; Krieg et al. 2013b). The preoperative localization of functional cortex may make more patients eligible for resection. While this localization would benefit relatively few patients with metastases, in which surgery is usually feasible irrespective of location, patients suffering from HGG and even more so from LGG could benefit significantly, as the preoperative nTMS map demonstrates the exact relationship between tumor and eloquent

cortex (Picht et al. 2012). More importantly, in cases of a highly eloquent tumor location, longitudinal follow-up with annual nTMS mappings could identify at some future time point when the risk of surgical resection becomes acceptable.

17.2.2 Detecting Functional Reorganization by nTMS Motor Mapping

Within the last years, reports are increasingly demonstrating that nTMS can identify functional reorganization and contribute significantly to the management of neuro-oncology patients.

In one case report, a patient suffering from a LGG within the hand knob of the precentral gyrus was initially deemed to have a nonresectable lesion. Preoperative nTMS mapping revealed motor areas to be outside the anatomically presumed motor eloquent cortex (Takahashi et al. 2012). This case was later supported by data from two other cases which showed comparable observations in two epilepsy patients (Makela et al. 2013).

These initial case reports are supported by larger investigations into the utility of nTMS in detecting relocation of motor function. In one study, the 3D data of nTMS motor maps of 100 brain tumor patients were fused (Bulubas et al. 2016) (Fig. 17.1). The authors found an extensive distribution of primary motor function with short-latency MEPs far beyond the precentral gyrus, but also different distributions of motor function depending on the location of the parenchymal brain tumor even within the precentral gyrus (Fig. 17.2).

Another recent study investigated the frequency and spatial pattern of functional reorganization in 22 glioma patients (Conway et al. 2017). After spatial normalization to account for brain shift, the authors reported an average shift of the CoG of M1 of 9.7 ± 1.5 mm (mean ± SEM) on the anteroposterior axis, a value outside the margin of error of the nTMS system and thus suggestive of significant change (Ruohonen and Karhu 2010).

These findings are supported by another study on healthy volunteers analyzing the optimal parameters for characterizing motor cortex plasticity with nTMS. This study found that rMT, CoG, as well as mean MEPs are reliable parameters showing high test-retest reliability for monitoring functional reorganization during longer follow-up (Kraus and Gharabaghi 2016).

Thus, the currently available data shows that (1) cortical functional reorganization occurs in LGG but also in HGG patients and (2) nTMS is able to detect such functional reorganization noninvasively.

Whether these data can also be used effectively in the clinical setting and what impact these data have on our treatment algorithms and outcomes are the major questions yet to be answered. Currently, the available patient cohorts are too small to observe statistically significant differences in frequency, time course, and extent of functional reorganization, considering the necessary stratification by tumor histology and neurological status. Answering these questions will require large multicenter and multinational approaches.

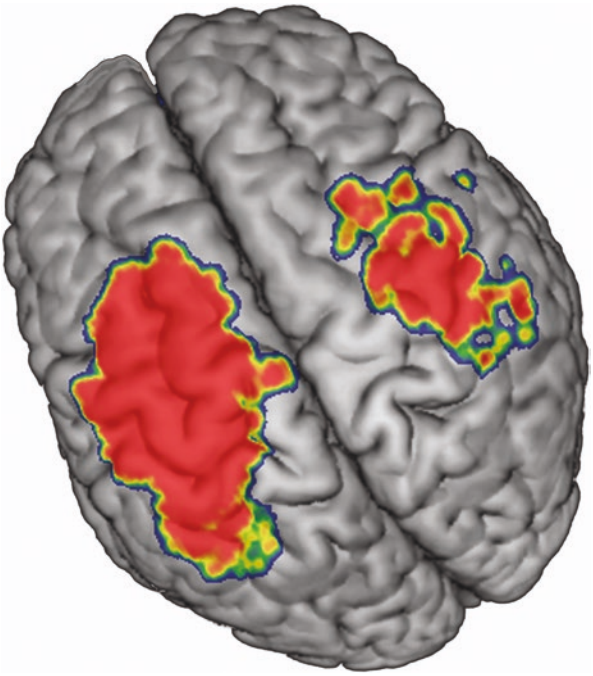

Fig. 17.1 Extensive motor areas as identified via nTMS. This is the result of normalization and fusion of the motor mapping data of 100 brain tumor patients. The motor area, in which MEPs were elicited, goes far frontal of the Rolandic region. This effect is even more emphasized in the (dominant) left hemisphere (Bulubas et al. 2016)

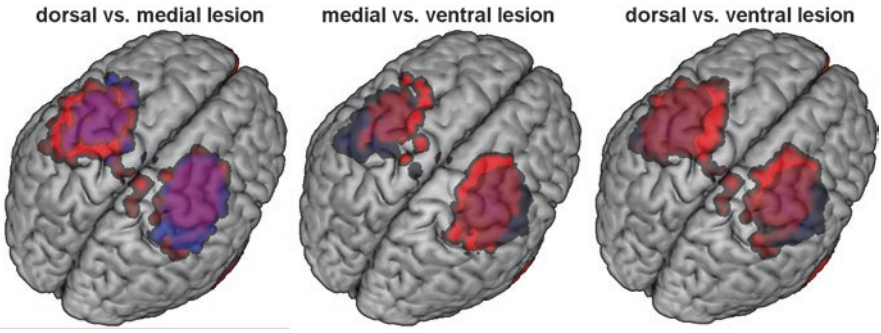

Fig. 17.2 Motor areas of tumors located inside the precentral gyrus. Patients with a tumor inside the precentral gyrus were divided into three groups depending on the tumor location (dorsal, medial, and ventral part of the precentral gyrus). For each group the motor mapping data were normalized and fused. Even between these groups, a difference in the pattern of motor function location can be observed (Bulubas et al. 2016)

17.2.3 Detecting Functional Reorganization by nrTMS Language Mapping

The right hemisphere has been shown to participate in language function not only in healthy participants (Vigneau et al. 2011; Schuhmann et al. 2012; Devlin and Watkins 2007; Brennan and Pylkkanen 2012) but also in patients after left hemispheric stroke (Baumgaertner et al. 2012; Baum et al. 2012) or brain tumor (Briganti et al. 2012; Perrone-Bertolotti et al. 2012; Bonelli et al. 2012; Wang et al. 2013; Thiel et al. 2005, 2006). These reports used a variety of methods, including neuropsychological assessment, nonnavigated TMS, and fMRI. The fMRI technique in particular can be confounded by intracerebral tumors and ischemic lesions (see Chap. 2 for a discussion on this point) (Giussani et al. 2010; Hou et al. 2006; Ille et al. 2015). Published nTMS-based studies of language laterality have demonstrated that right-handed patients harboring left-sided perisylvian brain tumors can experience a shift of language function to the right hemisphere, in contradistinction to healthy subjects (Krieg et al. 2013c). These results were later confirmed by a second nTMS research group (Rosler et al. 2014). These nrTMS studies corroborated studies using other modalities, as well as previous intraoperative data (Duffau 2006; Robles et al. 2008). We have also seen that functional reorganization not only causes a shift of language function to the contralateral hemisphere but also to other parts of the ipsilateral hemisphere (Kawashima et al. 2013; Krieg et al. 2014). Another study of 80 patients undergoing resection of left-sided perisylvian brain tumors showed that patients with more right-sided language have a lower risk of aphasia 5 days after tumor resection (Ille et al. 2016).

Finally, nrTMS language mapping allows for the longitudinal reexamination of patients with known tumors in high-risk regions. By following patients at regular intervals, nrTMS-based language mapping alerts the clinician when a previously unresectable tumor has become resectable due to the relocation of critical language sites (Krieg et al. 2014).

Notwithstanding the aforementioned capabilities of nrTMS language mapping, there remains much work in defining and refining the mapping protocols. The major areas of research on nrTMS language mapping are:

- Improving the PPV to increase the utility of positive site mapping
- Evaluating the usefulness of nrTMS language mapping for risk assessment (Chap. 10)
- Analyzing the utility of negative nrTMS language mapping in following the functional reorganization of language function

17.2.4 Mapping of Additional Neurocognitive Functions

Performing nTMS maps of other neurocognitive functions, such as arithmetic processing or visuospatial attention, can help to avoid common postoperative neuropsychological deficits. Such tasks can (and should) be tailored to the individual patient, based on the skillset that each patient wishes to preserve. It still remains to

be seen, how useful the nTMS maps of these higher-level neurocognitive functions will be in the clinical management of brain tumor patients. Evaluating and optimizing these studies will be a major issue in the development of nTMS. An extensive discussion of this topic may be found in Chap. 11.

17.3 Therapeutic Use: Inducing Functional Reorganization with nRTMS

17.3.1 General Considerations

Besides the therapeutic applications for chronic pain (Chap. 13), tinnitus, and depression, nrTMS has been found to enhance recovery of aphasia and paresis after stroke (Chap. 14). One mechanism for this effect is thought to be the induction of functional reorganization (Kim et al. 2006; Abo et al. 2014; Du et al. 2016). This theory is supported by various laboratory investigations showing that rTMS can induce plasticity on the synaptic and cellular level (Lenz et al. 2016; Korchounov and Ziemann 2011).

17.3.2 Treatment of Surgery-Related Deficits

Preliminary studies of nrTMS-based treatment after stroke have demonstrated an impressive improvement in motor deficits (Takeuchi et al. 2009; Abo et al. 2014; Kim et al. 2006; Takeuchi and Izumi 2012). Due to the fact that the majority of postoperative deficits also result from ischemic lesions (Fig. 17.3), it is reasonable to investigate whether nrTMS can also induce reorganization and facilitate recovery in

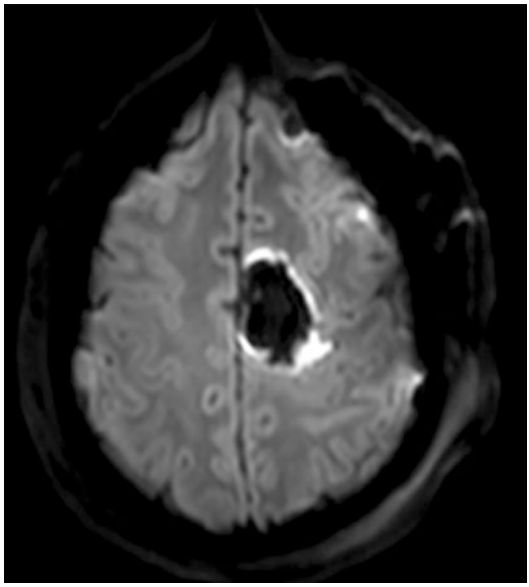

Fig. 17.3 Candidate for postoperative nrTMS treatment. This axial DWI slide shows a patient after resection of an anaplastic astrocytoma WHO III in the SFG suffering from a severe surgery-related paresis of the right hand due to ischemia in the precentral gyrus. These patients are highly comparable to stroke patients who repeatedly showed to benefit from nrTMS treatment

neurosurgical patients with postoperative deficits (Krieg et al. 2012, 2013a; Gempt et al. 2013; Obermueller et al. 2014). In an unpublished feasibility study, brain tumor patients with postoperative impairment of motor or language function tolerated 7 days of nrTMS therapy, even if started on the first postoperative day. Larger clinical trials on the postoperative use of nrTMS treatment for surgery-related deficits are ongoing and represent a promising application of this technology.

17.3.3 Prehabilitation: Preoperative Induction of Functional Reorganization

Rather than waiting for a tumor to induce functional reorganization, prehabilitation uses nrTMS to try and move functionally eloquent brain regions away from a planned surgical site (Fig. 17.4). To date, there are only three published case reports on this technique; nevertheless, these reports provide proof of concept and valuable data for the noninvasive induction of functional reorganization by nrTMS. In all three cases, using a protocol of 7–12 sessions of nrTMS therapy for 10–20 min each day, the investigators were able to modify the organization of language networks (Barwood et al. 2011; Andoh and Martinot 2008; Barcia et al. 2012).

Barcia et al. reported on a glioma patient who underwent incomplete resection due to intraoperatively identified eloquent brain tissue within the tumor. The patient underwent intralesional treatment with nrTMS. After each session, the patient experienced worsened language function, but this effect lessened over the course of 12 sessions. This change was interpreted as a functional reorganization of language function away from the previously identified brain area (Barcia et al. 2012). Two other groups obtained comparable results (Barwood et al. 2011; Andoh and Martinot 2008). Of note, nrTMS is used in each of these three reports and is the only reported noninvasive method for inducing functional reorganization.

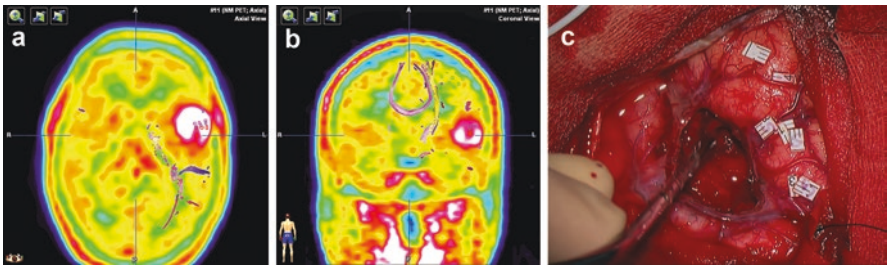

Fig. 17.4 Candidate for preoperative prehabilitation by nrTMS treatment. These axial (**a**) and coronal (**b**) slides show the fusion of a preoperative PET scan and preoperative nTMS/nrTMS motor and language mapping in a bilingual patient suffering from an anaplastic astrocytoma WHO III in the triangular part of the left IFG. The nrTMS mapping shows language-involved cortex right inside the upper part of the tumor for both languages, which was later confirmed during awake surgery by DES mapping (**c**). Prehabilitation could be applied to move language function outside the tumor. Language mapping of language-negative cortex could monitor the success of prehabilitation and therefore confirm the time point of optimal second resective surgery going for GTR

Even using invasive techniques, there is only one reported series of prehabilitation. Barcia and colleagues induced functional reorganization in five out of five patients by applying high-frequency stimulation via implanted subdural grid electrodes for 27–37 days (Rivera-Rivera et al. 2016). They found a shift of language function to the contralateral hemisphere (as assessed with fMRI) after stimulation. Nevertheless, the reported rate of severe complications was 60% (two patients with brain infection, one patient with severe intracranial hemorrhage). This rate is unacceptably high for the technique to be applied broadly. The nrTMS treatment, which is noninvasive and carries minimal risk, may have the same capability, but without the ethical concerns.

17.4 Conclusion

With each passing year and each additional study, the application of nTMS in neurosurgery becomes increasingly exciting. The future may allow us to map neurological functions other than motor and language; it may also enable us to follow functional reorganization and use this information to optimize the timing of an intervention in neuro-oncological pathology. Moreover, the therapeutic use of nrTMS for prehabilitation and treatment of postoperative deficits may be a transformative new technique for clinical neurosurgery.

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