Brain Plasticity in Neurosurgery

16

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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
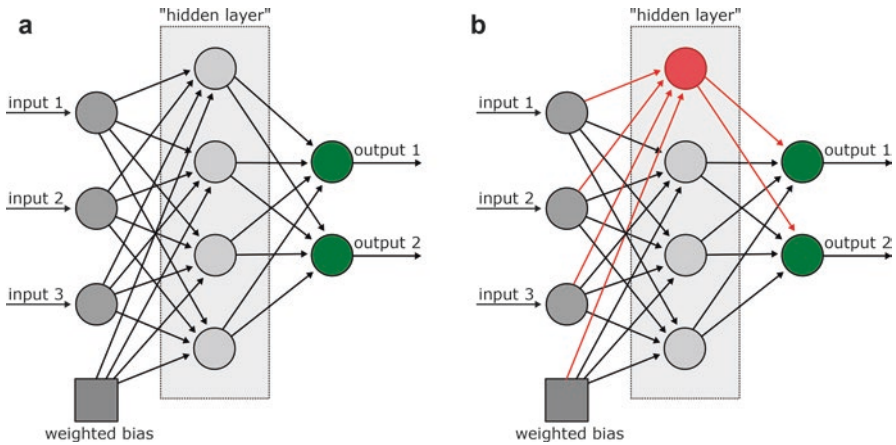
Fig. 16.1 Neural network example of normally functioning (**a**) and lesioned network (**b**) and resulting modulation of network function adapting to impairment in parts of the network. The neural network represents a simplistic view of a functional network of neurons in the brain, which has an input 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).
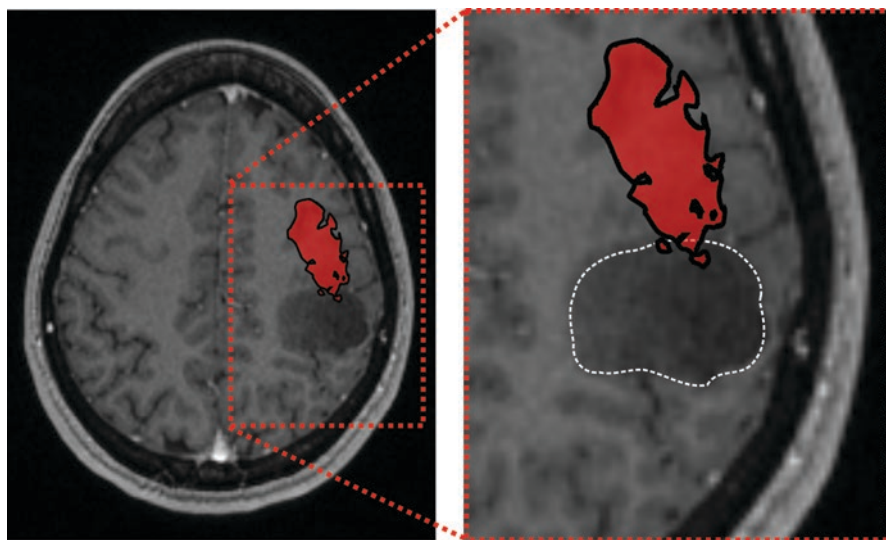
Fig. 16.2 Example of an outlined cortical map of hand muscle function on the M1 overlaid on an axial MRI slice. The functional area is represented as *red*, and the tumor and affected anatomical structure is outlined with a *white dashed line* in the close-up on the right. Outlining was performed using 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).
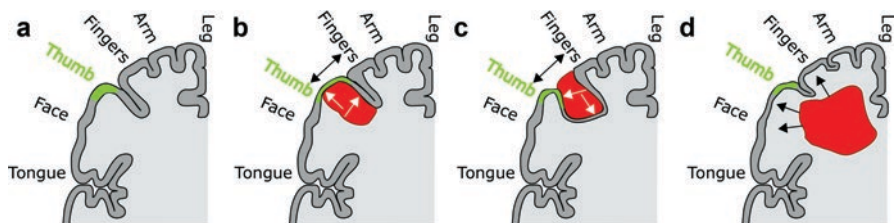
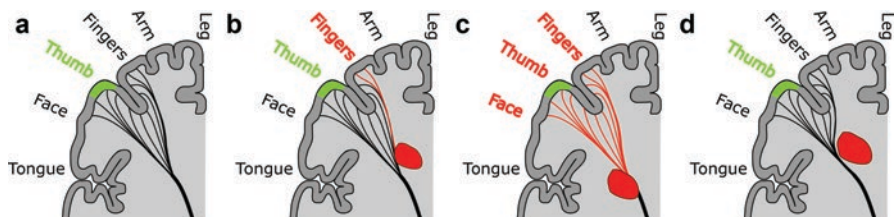**Fig. 16.3** Effect of lesion growth within M1 represented in simplified schematic images. In the images, a coronal view is used for 2D visualization of the common homunculus for simplicity reasons. (**a**) Normal, intact brain in adult human subjects. Functional area of the thumb is highlighted in *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
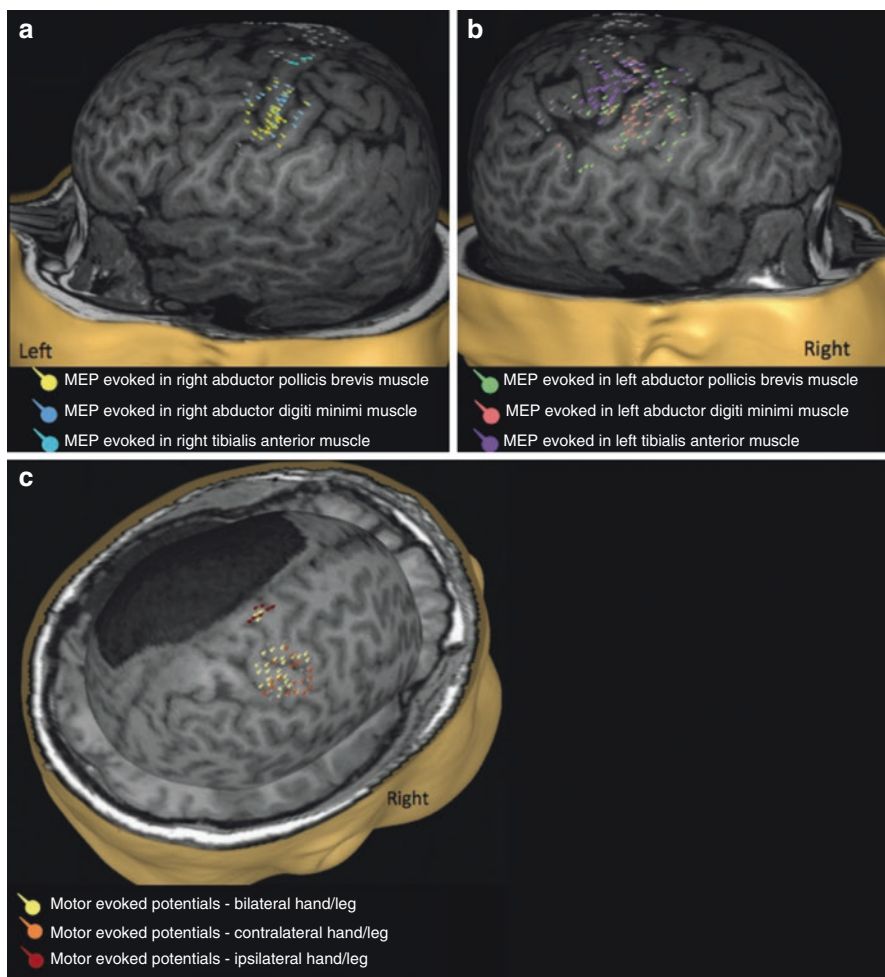
Fig. 16.5 Functional reorganization of the motor cortex. (**a**) nTMS motor mapping demonstrating the effect of cortical dysplasia on cortical functional reorganization in a 13-year-old girl. Normal organization of the left motor cortex with normal cortical localization of the right hand and leg. (**b**) 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
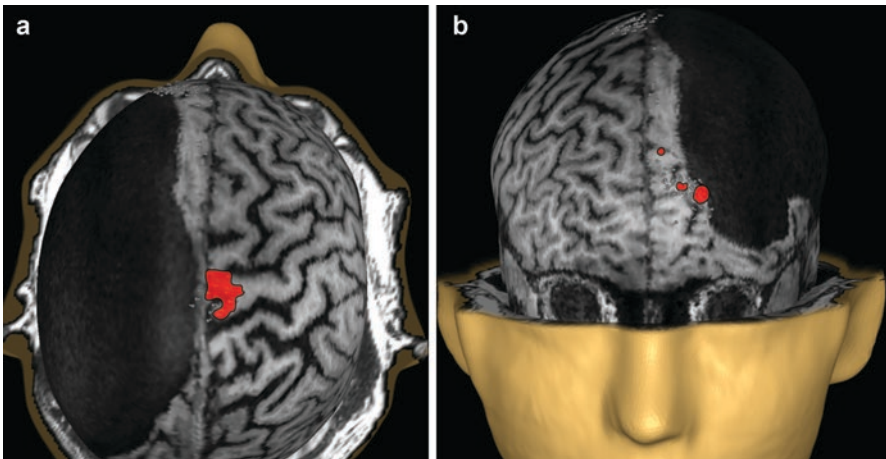

Fig. 16.6 Functional reorganization after stroke. (**a**) Left-foot and (**b**) right-foot muscle representation revealed by nTMS mapping in a 19-year-old male epilepsy patient with right-sided hemiparesis and an extensive perinatal vascular infarction in the left middle cerebral artery territory. Sites 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.
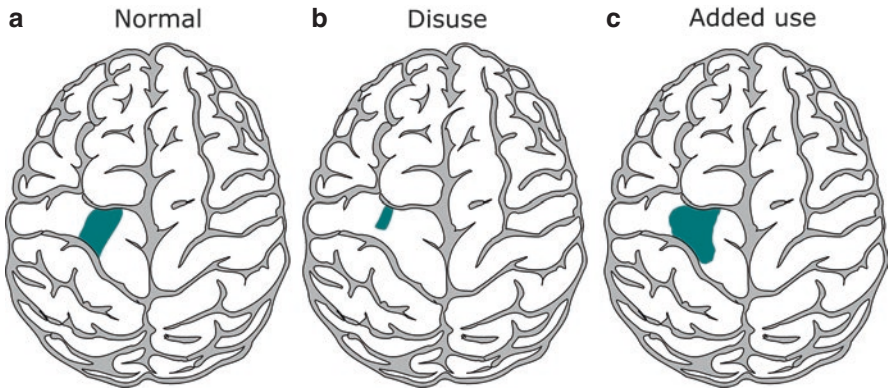
Fig. 16.7 Use-dependent plasticity. Schematic example of potential effects of use-dependent plasticity on functional hand motor area of the M1. (**a**) Normal representation area (as *green*). (**b**) Effects of long-term disuse of the muscle result in reduction of size of the functional motor area (Liepert 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.

References

Abdul-Kareem IA, Stancak A, Parkes LM, Sluming V. Increased gray matter volume of left pars opercularis in male orchestral musicians correlate positively with years of musical performance. J Magn Reson Imaging. 2011;33(1):24–32. doi:10.1002/jmri.22391.

Adkins DL, Boychuk J, Remple MS, Kleim JA. Motor training induces experience-specific patterns of plasticity across motor cortex and spinal cord. J Appl Physiol (1985). 2006;101(6):1776–82. doi:10.1152/japplphysiol.00515.2006.

Bangert M, Schlaug G. Specialization of the specialized in features of external human brain morphology. Eur J Neurosci. 2006;24(6):1832–4. doi:10.1111/j.1460-9568.2006.05031.x.

Bavelier D, Neville HJ. Cross-modal plasticity: where and how? Nat Rev Neurosci. 2002;3(6):443–52. doi:10.1038/nrn848.

Borghetti D, Sartucci F, Petacchi E, Guzzetta A, Piras MF, Murri L, et al. Transcranial magnetic stimulation mapping: a model based on spline interpolation. Brain Res Bull. 2008;77(2–3):143–8. doi:10.1016/j.brainresbull.2008.06.001.

Byrnes ML, Thickbroom GW, Wilson SA, Sacco P, Shipman JM, Stell R, et al. The corticomotor representation of upper limb muscles in writer's cramp and changes following botulinum toxin injection. Brain. 1998;121(Pt 5):977–88.

Classen J, Knorr U, Werhahn KJ, Schlaug G, Kunesch E, Cohen LG, et al. Multimodal output mapping of human central motor representation on different spatial scales. J Physiol. 1998;512(Pt 1):163–79.

Conti A, Pontoriero A, Ricciardi GK, Granata F, Vinci S, Angileri FF, et al. Integration of functional neuroimaging in CyberKnife radiosurgery: feasibility and dosimetric results. Neurosurg Focus. 2013;34(4):E5. doi:10.3171/2013.2.FOCUS12414.

Conti A, Raffa G, Granata F, Rizzo V, Germano A, Tomasello F. Navigated transcranial magnetic stimulation for "somatotopic" tractography of the corticospinal tract. Neurosurgery. 2014;10(Suppl 4):542–554.; discussion 554. doi:10.1227/NEU.0000000000000502.

Conway N, Tanigawa N, Meyer B, Krieg SM. Cortical plasticity of motor-eloquent areas measured by navigated transcranial magnetic stimulation in glioma patients. Neurosurgery. 2016;63(Suppl 1):207–8. doi:10.1227/01.neu.0000489851.39946.4c.

Danner N, Könönen M, Säisänen L, Laitinen R, Mervaala E, Julkunen P. Effect of individual anatomy on resting motor threshold-computed electric field as a measure of cortical excitability. J Neurosci Methods. 2012;203(2):298–304. doi:10.1016/j.jneumeth.2011.10.004.

Desmurget M, Bonnetblanc F, Duffau H. Contrasting acute and slow-growing lesions: a new door to brain plasticity. Brain. 2007;130(Pt 4):898–914. doi:10.1093/brain/awl300.

Di Pino G, Pellegrino G, Assenza G, Capone F, Ferreri F, Formica D, et al. Modulation of brain plasticity in stroke: a novel model for neurorehabilitation. Nat Rev Neurol. 2014;10(10):597–608. doi:10.1038/nrneurol.2014.162.

Duffau H. Lessons from brain mapping in surgery for low-grade glioma: insights into associations between tumour and brain plasticity. Lancet Neurol. 2005;4(8):476–86. doi:10.1016/S1474-4422(05)70140-X.

Duffau H. Brain plasticity: from pathophysiological mechanisms to therapeutic applications. J Clin Neurosci. 2006;13(9):885–97. doi:10.1016/j.jocn.2005.11.045.

Duffau H, Sichez JP, Lehericy S. Intraoperative unmasking of brain redundant motor sites during resection of a precentral angioma: evidence using direct cortical stimulation. Ann Neurol. 2000;47(1):132–5.

Elbert T, Rockstroh B. Reorganization of human cerebral cortex: the range of changes following use and injury. Neuroscientist. 2004;10(2):129–41. doi:10.1177/1073858403262111.

Elbert T, Pantev C, Wienbruch C, Rockstroh B, Taub E. Increased cortical representation of the fingers of the left hand in string players. Science. 1995;270(5234):305–7.

Foltys H, Krings T, Meister IG, Sparing R, Boroojerdi B, Thron A, et al. Motor representation in patients rapidly recovering after stroke: a functional magnetic resonance imaging and transcranial magnetic stimulation study. Clin Neurophysiol. 2003;114(12):2404–15.

Forster MT, Senft C, Hattingen E, Lorei M, Seifert V, Szelenyi A. Motor cortex evaluation by nTMS after surgery of central region tumors: a feasibility study. Acta Neurochir. 2012;154(8):1351–9. doi:10.1007/s00701-012-1403-4.

Freund P, Rothwell J, Craggs M, Thompson AJ, Bestmann S. Corticomotor representation to a human forearm muscle changes following cervical spinal cord injury. Eur J Neurosci. 2011;34(11):1839–46. doi:10.1111/j.1460-9568.2011.07895.x.

Frey D, Strack V, Wiener E, Jussen D, Vajkoczy P, Picht T. A new approach for corticospinal tract reconstruction based on navigated transcranial stimulation and standardized fractional anisotropy values. Neuroimage. 2012;62(3):1600–9. doi:10.1016/j.neuroimage.2012.05.059.

Gagne M, Hetu S, Reilly KT, Mercier C. The map is not the territory: motor system reorganization in upper limb amputees. Hum Brain Mapp. 2011;32(4):509–19. doi:10.1002/hbm.21038.

Guggisberg AG, Honma SM, Findlay AM, Dalal SS, Kirsch HE, Berger MS, et al. Mapping functional connectivity in patients with brain lesions. Ann Neurol. 2008;63(2):193–203. doi:10.1002/ana.21224.

Hebb DO. Organization of Behavior. New York: John Wiley & Sons, Inc.; 1949.

Hetu S, Gagne M, Reilly KT, Mercier C. Short-term reliability of transcranial magnetic stimulation motor maps in upper limb amputees. J Clin Neurosci. 2011;18(5):728–30. doi:10.1016/j.jocn.2010.09.011.

Ius T, Angelini E, Thiebaut de Schotten M, Mandonnet E, Duffau H. Evidence for potentials and limitations of brain plasticity using an atlas of functional resectability of WHO grade II gliomas: towards a "minimal common brain". Neuroimage. 2011;56(3):992–1000. doi:10.1016/j.neuroimage.2011.03.022. S1053-8119(11)00283-7 [pii]

Julkunen P. Methods for estimating cortical motor representation size and location in navigated transcranial magnetic stimulation. J Neurosci Methods. 2014;232:125–33. doi:10.1016/j.jneumeth.2014.05.020.

Julkunen P, Säisänen L, Danner N, Awiszus F, Könönen M. Within-subject effect of coil-to-cortex distance on cortical electric field threshold and motor evoked potentials in transcranial magnetic stimulation. J Neurosci Methods. 2012;206(2):158–64. doi:10.1016/j.jneumeth.2012.02.020.

Julkunen P, Könönen M, Määttä S, Tarkka IM, Hiekkala SH, Säisänen L, et al. Longitudinal study on modulated corticospinal excitability throughout recovery in supratentorial stroke. Neurosci Lett. 2016a;617:88–93. doi:10.1016/j.neulet.2016.02.014.

Julkunen P, Määttä S, Säisänen L, Kallioniemi E, Könönen M, Jäkälä P, et al. Functional and structural cortical characteristics after restricted focal motor cortical infarction evaluated at chronic stage – indications from a preliminary study. Clin Neurophysiol. 2016b;127(8):2775–84. doi:10.1016/j.clinph.2016.05.013.

Jussen D, Zdunczyk A, Schmidt S, Rosler J, Buchert R, Julkunen P, et al. Motor plasticity after extra-intracranial bypass surgery in occlusive cerebrovascular disease. Neurology. 2016;87(1):27–35. doi:10.1212/WNL.0000000000002802.

Kaas JH. Functional plasticity in adult cortex, vol. 8. Orlando: Academic Press; 1997.

Kallioniemi E, Julkunen P. Alternative stimulation intensities for mapping cortical motor area with navigated TMS. Brain Topogr. 2016;29(3):395–404. doi:10.1007/s10548-016-0470-x.

Kallioniemi E, Könönen M, Säisänen L, Gröhn H, Julkunen P. Functional neuronal anisotropy assessed with neuronavigated transcranial magnetic stimulation. J Neurosci Methods. 2015; 256:82–90. doi:10.1016/j.jneumeth.2015.08.028.

Kallioniemi E, Pitkänen M, Könönen M, Vanninen R, Julkunen P. Localization of cortical primary motor area of the hand using navigated transcranial magnetic stimulation, BOLD and arterial spin labeling fMRI. J Neurosci Methods. 2016;273:138–48. doi:10.1016/j.jneumeth. 2016.09.002.

Kamada K, Todo T, Masutani Y, Aoki S, Ino K, Morita A, et al. Visualization of the frontotemporal language fibers by tractography combined with functional magnetic resonance imaging and magnetoencephalography. J Neurosurg. 2007;106(1):90–8. doi:10.3171/jns.2007.106.1.90.

Kato N, Schilt S, Schneider H, Frey D, Kufeld M, Vajkoczy P, et al. Functional brain mapping of patients with arteriovenous malformations using navigated transcranial magnetic stimulation: first experience in ten patients. Acta Neurochir. 2014;156(5):885–95. doi:10.1007/s00701-014-2043-7.

Keidel JL, Welbourne SR, Lambon Ralph MA. Solving the paradox of the equipotential and modular brain: a neurocomputational model of stroke vs. slow-growing glioma. Neuropsychologia. 2010;48(6):1716–24. doi:10.1016/j.neuropsychologia.2010.02.019.

Kesar TM, Sawaki L, Burdette JH, Cabrera MN, Kolaski K, Smith BP, et al. Motor cortical functional geometry in cerebral palsy and its relationship to disability. Clin Neurophysiol. 2012;123(7):1383–90. doi:10.1016/j.clinph.2011.11.005.

Koch C. Biophysics of computation: information processing in single neurons. New York: Oxford University Press; 1998.

Krieg SM, Sollmann N, Hauck T, Ille S, Foerschler A, Meyer B, et al. Functional language shift to the right hemisphere in patients with language-eloquent brain tumors. PLoS One. 2013;8(9):e75403. doi:10.1371/journal.pone.0075403.

Labyt E, Houdayer E, Cassim F, Bourriez JL, Derambure P, Devanne H. Motor representation areas in epileptic patients with focal motor seizures: a TMS study. Epilepsy Res. 2007;75(2–3): 197–205. doi:10.1016/j.eplepsyres.2007.06.004.

Langguth B, Eichhammer P, Zowe M, Kleinjung T, Jacob P, Binder H, et al. Altered motor cortex excitability in tinnitus patients: a hint at crossmodal plasticity. Neurosci Lett. 2005;380(3):326–9. doi:10.1016/j.neulet.2005.01.069.

Laughlin SB, Sejnowski TJ. Communication in neuronal networks. Science. 2003;301(5641):1870–4. doi:10.1126/science.1089662.

Lefaucheur JP, Picht T. The value of preoperative functional cortical mapping using navigated TMS. Neurophysiol Clin. 2016;46(2):125–33. doi:10.1016/j.neucli.2016.05.001.

Lehericy S, Biondi A, Sourour N, Vlaicu M, du Montcel ST, Cohen L, et al. Arteriovenous brain malformations: is functional MR imaging reliable for studying language reorganization in patients? Initial observations. Radiology. 2002;223(3):672–82. doi:10.1148/radiol.2233010792.

Liepert J, Tegenthoff M, Malin JP. Changes of cortical motor area size during immobilization. Electroencephalogr Clin Neurophysiol. 1995;97(6):382–6.

Majos A, Bryszewski B, Kosla KN, Pfaifer L, Jaskolski D, Stefanczyk L. Process of the functional reorganization of the cortical centers for movement in GBM patients: fMRI study. Clin Neuroradiol. 2015; doi:10.1007/s00062-015-0398-7.

Mäkelä JP, Vitikainen AM, Lioumis P, Paetau R, Ahtola E, Kuusela L, et al. Functional plasticity of the motor cortical structures demonstrated by navigated TMS in two patients with epilepsy. Brain Stimul. 2013;6(3):286–91. doi:10.1016/j.brs.2012.04.012.

Mäkelä JP, Lioumis P, Laaksonen K, Forss N, Tatlisumak T, Kaste M, et al. Cortical excitability measured with nTMS and MEG during stroke recovery. Neural Plast. 2015;2015:309546. doi:10.1155/2015/309546.

Malcolm MP, Triggs WJ, Light KE, Shechtman O, Khandekar G, Gonzalez Rothi LJ. Reliability of motor cortex transcranial magnetic stimulation in four muscle representations. Clin Neurophysiol. 2006;117(5):1037–46. doi:10.1016/j.clinph.2006.02.005.

Muellbacher W, Ziemann U, Boroojerdi B, Cohen L, Hallett M. Role of the human motor cortex in rapid motor learning. Exp Brain Res. 2001;136(4):431–8.

Muller-Dahlhaus F, Vlachos A. Unraveling the cellular and molecular mechanisms of repetitive magnetic stimulation. Front Mol Neurosci. 2013;6:50. doi:10.3389/fnmol.2013.00050.

Narayana S, Papanicolaou AC, McGregor A, Boop FA, Wheless JW. Clinical applications of transcranial magnetic stimulation in pediatric neurology. J Child Neurol. 2015;30(9):1111–24. doi:10.1177/0883073814553274.

Negwer C, Sollmann N, Ille S, Hauck T, Maurer S, Kirschke JS, et al. Language pathway tracking: comparing nTMS-based DTI fiber tracking with a cubic ROIs-based protocol. J Neurosurg. 2016:1–9. doi:10.3171/2016.2.JNS152382.

Otsubo H, Iida K, Oishi M, Okuda C, Ochi A, Pang E, et al. Neurophysiologic findings of neuronal migration disorders: intrinsic epileptogenicity of focal cortical dysplasia on electroencephalography, electrocorticography, and magnetoencephalography. J Child Neurol. 2005;20(4):357–63.

Papagno C, Gallucci M, Casarotti A, Castellano A, Falini A, Fava E, et al. Connectivity constraints on cortical reorganization of neural circuits involved in object naming. Neuroimage. 2011;55(3):1306–13. doi:10.1016/j.neuroimage.2011.01.005.

Pascual-Leone A, Grafman J, Hallett M. Modulation of cortical motor output maps during development of implicit and explicit knowledge. Science. 1994;263(5151):1287–9.

Pascual-Leone A, Nguyet D, Cohen LG, Brasil-Neto JP, Cammarota A, Hallett M. Modulation of muscle responses evoked by transcranial magnetic stimulation during the acquisition of new fine motor skills. J Neurophysiol. 1995;74(3):1037–45.

Pascual-Leone A, Amedi A, Fregni F, Merabet LB. The plastic human brain cortex. Annu Rev Neurosci. 2005;28:377–401. doi:10.1146/annurev.neuro.27.070203.144216.

Pearce AJ, Thickbroom GW, Byrnes ML, Mastaglia FL. Functional reorganisation of the corticomotor projection to the hand in skilled racquet players. Exp Brain Res. 2000;130(2):238–43.

Picht T, Mularski S, Kuehn B, Vajkoczy P, Kombos T, Suess O. Navigated transcranial magnetic stimulation for preoperative functional diagnostics in brain tumor surgery. Neurosurgery. 2009;65(6 Suppl):93–8.

Pihko E, Nevalainen P, Vaalto S, Laaksonen K, Mäenpää H, Valanne L, et al. Reactivity of sensorimotor oscillations is altered in children with hemiplegic cerebral palsy: a magnetoencephalographic study. Hum Brain Mapp. 2014;35(8):4105–17. doi:10.1002/hbm.22462.

Pitkänen M, Kallioniemi E, Julkunen P. Extent and location of the excitatory and inhibitory cortical hand representation maps: a navigated transcranial magnetic stimulation study. Brain Topogr. 2015;28(5):657–65. doi:10.1007/s10548-015-0442-6.

Pouratian N, Bookheimer SY. The reliability of neuroanatomy as a predictor of eloquence: a review. Neurosurg Focus. 2010;28(2):E3. doi:10.3171/2009.11.FOCUS09239.

Rosenkranz K, Williamon A, Rothwell JC. Motorcortical excitability and synaptic plasticity is enhanced in professional musicians. J Neurosci. 2007;27(19):5200–6. doi:10.1523/JNEUROSCI.0836-07.2007.

Rösler J, Niraula B, Strack V, Zdunczyk A, Schilt S, Savolainen P, et al. Language mapping in healthy volunteers and brain tumor patients with a novel navigated TMS system: evidence of tumor-induced plasticity. Clin Neurophysiol. 2014;125(3):526–36. doi:10.1016/j.clinph.2013.08.015.

Rossini PM, Calautti C, Pauri F, Baron JC. Post-stroke plastic reorganisation in the adult brain. Lancet Neurol. 2003;2(8):493–502.

Ruohonen J, Karhu J. Navigated transcranial magnetic stimulation. Neurophysiol Clin. 2010;40(1):7–17. doi:10.1016/j.neucli.2010.01.006.

Säisänen L, Könönen M, Julkunen P, Määttä S, Vanninen R, Immonen A, et al. Non-invasive preoperative localization of primary motor cortex in epilepsy surgery by navigated transcranial magnetic stimulation. Epilepsy Res. 2010;92(2–3):134–44. doi:10.1016/j.eplepsyres.2010.08.013.

Schieber MH, Hibbard LS. How somatotopic is the motor cortex hand area? Science. 1993;261(5120):489–92.

Schmidt S, Bathe-Peters R, Fleischmann R, Ronnefarth M, Scholz M, Brandt SA. Nonphysiological factors in navigated TMS studies; confounding covariates and valid intracortical estimates. Hum Brain Mapp. 2015;36(1):40–9. doi:10.1002/hbm.22611.

Siebner HR, Rothwell J. Transcranial magnetic stimulation: new insights into representational cortical plasticity. Exp Brain Res. 2003;148(1):1–16. doi:10.1007/s00221-002-1234-2.

Sisodiya SM, Fauser S, Cross JH, Thom M. Focal cortical dysplasia type II: biological features and clinical perspectives. Lancet Neurol. 2009;8(9):830–43. doi:10.1016/S1474-4422(09)70201-7.

Sluming V, Barrick T, Howard M, Cezayirli E, Mayes A, Roberts N. Voxel-based morphometry reveals increased gray matter density in Broca's area in male symphony orchestra musicians. Neuroimage. 2002;17(3):1613–22.

Smits A, Zetterling M, Lundin M, Melin B, Fahlstrom M, Grabowska A, et al. Neurological impairment linked with cortico-subcortical infiltration of diffuse low-grade gliomas at initial diagnosis supports early brain plasticity. Front Neurol. 2015;6:137. doi:10.3389/fneur.2015.00137.

Szalisznyo K, Silverstein DN, Duffau H, Smits A. Pathological neural attractor dynamics in slowly growing gliomas supports an optimal time frame for white matter plasticity. PLoS One. 2013;8(7):e69798. doi:10.1371/journal.pone.0069798.

Takahashi S, Jussen D, Vajkoczy P, Picht T. Plastic relocation of motor cortex in a patient with LGG (low grade glioma) confirmed by NBS (navigated brain stimulation). Acta Neurochir. 2012;154(11):2003–8. doi:10.1007/s00701-012-1492-0.

Tyc F, Boyadjian A, Devanne H. Motor cortex plasticity induced by extensive training revealed by transcranial magnetic stimulation in human. Eur J Neurosci. 2005;21(1):259–66. doi:10.1111/j.1460-9568.2004.03835.x.

Vaalto S, Julkunen P, Säisänen L, Könönen M, Määttä S, Karhu J. Long-term plasticity may be manifested as reduction or expansion of cortical representations of actively used muscles in motor skill specialists. Neuroreport. 2013;24(11):596–600. doi:10.1097/WNR.0b013e3283628636.

Vikingstad EM, Cao Y, Thomas AJ, Johnson AF, Malik GM, Welch KM. Language hemispheric dominance in patients with congenital lesions of eloquent brain. Neurosurgery. 2000;47(3):562–70.

Wassermann EM, McShane LM, Hallett M, Cohen LG. Noninvasive mapping of muscle representations in human motor cortex. Electroencephalogr Clin Neurophysiol. 1992;85(1):1–8.