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Transcranial Brain Stimulation: Clinical Applications and Future Directions

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In human brain mapping, 2 basic strategies are commonly used to obtain information about cortical functional representation: (1) recording brain activity during task performance (the passive approach) and (2) observing the effects of eliciting/extinguishing brain activity (the active approach).[1] Techniques using the passive approach include magnetoencephalography (MEG) and electroencephalography (EEG), which provide direct measures of neuronal activity, and positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), which capture brain hemodynamic and metabolic responses as indirect measures of neuronal activation. For the most part, such approaches fail to provide information about causal relationships between certain cortical regions and behavior or cognition. Furthermore, all these techniques are generally based on changes in brain activity that occur during task performance, and therefore depend on collaboration of the individual and careful behavioral assessments. Resting-state fMRI or EEG measures[2] are valuable, novel approaches to studying brain connectivity and network activity, but their usefulness in cortical output mapping is unclear. On the other hand, the active approach minimizes dependency on the individual's cooperation, because external stimuli are used to elicit or extinguish brain activity, although state-dependent influences on the effects of and responses to brain stimulation need to be considered and controlled for.[3] The active approach investigates whether a specific region of the brain is critical for implementing particular cognitive or behavioral functions and therefore is able to answer questions about causal relationships between brain and function. Noninvasive techniques using such an approach include transcranial electric stimulation (TES) and transcranial magnetic stimulation (TMS).

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The noninvasive approach has the advantage of having a greater safety profile and low cost burden for the patients (detailed safety considerations are discussed in later sections). Because of the noninvasiveness of such approaches, they can be repeated as desired, and because stimulation-naive patients get acclimatized to such stimulation techniques quickly, the stress confounders are limited. There is also the added benefit of the lack of medication confounders because most of the noninvasive approaches are based on the underlying activation threshold, thus controlling for the effects of medications on cortical excitability. However, in recent years brain-mapping studies using the passive approach have outnumbered those using the active approach. This situation has been in part because of the problems in correlating the site of stimulation noninvasively to the stimulated cortical region and in part because of the lack of focality of the available noninvasive stimulation devices. The advent of navigated TMS (nTMS) systems has significantly increased the usefulness of TMS in cortical mapping. Such systems can be easily recalibrated after patient movement and, during each stimulation train, the angle and the position of the coil on the scalp can be held constant as verified by real-time visual guidance using the navigation. Using navigation, TMS is able to provide precise information related to the individual's functional anatomy that can be visualized and used during surgical interventions and critically aid in presurgical planning, reducing the need for riskier and more cumbersome intraoperative or invasive mapping procedures. This article reviews the methodological aspects and clinical applications of noninvasive, brain-stimulation-based mapping.

HISTORICAL BACKGROUND

The realization that stimulating/mapping brain areas can guide surgical interventions dates back to Hughlings Jackson, who speculated that the cortex around the central sulcus contained an organized representation of body movements. He suggested that there was a discrete representation of movements of different body parts in this area, and that irritation could produce movements of the corresponding part of the contralateral body. This notion was later confirmed by Fritsch and Hitzig, and then by David Ferrier in the 1870s, who showed that electrical stimulation of the central area in dogs and monkeys could produce movements of the opposite side of the body. Bartholow[4] performed the first stimulation of the human motor cortex a few years later in a patient whose cortex was exposed by a large ulcer on her scalp. This cortical organization was later popularized in the now familiar motor homunculus drawn by Penfield and coworkers (Fig. 1).[5,6]

The work of Penfield and colleagues established invasive cortical mapping as a standard tool to investigate cortical organization. However, the limited resolution of the early cortical surface stimulation techniques led to the development of better and more advanced stimulation methods such as intracortical microstimulation (ICMS). Nevertheless, all such techniques remained invasive. With the advancement in noninvasive methods of brain stimulation, techniques such as TMS can now be used to leverage the same principle but do so noninvasively, with minimal discomfort to the patients.

Noninvasive brain stimulation provides a valuable tool for interventional neurophysiology applications, modulating brain activity in a specific, distributed, corticosubcortical network so as to induce controlled and controllable manipulations in behavior, as well as for focal neuropharmacology delivery, through the release of neurotransmitters in specific neural networks and the induction of focal gene expression, which may yield a specific behavioral effect. Noninvasive brain stimulation is also a promising treatment of a variety of medical conditions, and the number of applications continues to increase with the large number of ongoing clinical trials in a variety of diseases. Therapeutic usefulness of noninvasive brain stimulation has been claimed in the literature for psychiatric disorders, such as depression, acute mania, bipolar disorders, hallucinations, obsessions, schizophrenia, catatonia,

posttraumatic stress disorder, or drug craving; neurologic diseases, such as Parkinson disease (PD), dystonia, tics, stuttering, tinnitus, spasticity, or epilepsy; rehabilitation of aphasia or of hand function after stroke; and pain syndromes, such as those caused by migraine, neuropathies, and low-back pain; or internal visceral diseases, such as chronic pancreatitis or cancer. Although such claims are insufficiently supported by clinical trial data, the potential significance of noninvasive brain stimulation is huge, affecting a large number of patients with debilitating conditions.

In the realm of cortical mapping, the 2 most commonly used techniques for noninvasive brain stimulation are TES and TMS (Fig. 2). Such stimulation of the corticobulbar and corticospinal tracts within the brain are used for intraoperative monitoring and for extraoperative diagnostic assessment of central motor pathways. TMS is more useful for extraoperative diagnostic motor-evoked potential (MEP) studies as well as research applications to establish and map causal brain-behavior relations in nonmotor cortical areas. Both TES and TMS depolarize neurons by producing an electrical current within brain parenchyma, although the ways in which these intraparenchymal currents are generated are different. The advantage of TMS is that it does not activate scalp pain fibers as strongly as TES, and it is therefore useful for assessing central motor pathways in conscious individuals. Furthermore, TMS can also be applied to nonmotor regions in the brain convexity. This article focuses on the methodological aspects and clinical application of TMS in cortical mapping.

TMS

TMS mapping of cortical motor areas follows the basic principles of Penfield, and is based on the idea of stimulating different regions of the brain and measuring the modulatory effect (which can be either excitatory or inhibitory). TMS is a noninvasive technique that uses magnetic stimulation to generate electrical current in the cerebral cortex via a device that generates a brief electric current in a coil placed near the patient's head. The electric current in the coil in turn creates a magnetic-field variation of 1.5 to 2 T, which penetrates the skull to about 1.5 to 2.0 cm and reaches the brain. The magnetic field then produces currents changing at rates up to 170 A/μs and induces electric fields in the cortex of up to about 150 V/m. Thus, via electromagnetic induction, TMS painlessly induces ions to flow in the brain without exposing the skull to an electric current.

TMS with a focal figure-of-eight coil can be used to show the gross somatotopy of the motor homunculus. Stimuli are applied at various scalp sites using a latitude/longitude-based coordinate system referenced to the vertex,[7] and the amplitude of MEPs, recorded via electromyography (EMG), evoked in contralateral muscles is measured. This process gives a map of sites on the scalp from which responses can be obtained in each muscle of interest. Specifically, the MEP amplitude data recorded at discrete sites over the motor cortex are transformed to a continuously defined function such that the intermediate values are estimated[7,8] (see article by Thickbroom on mapping elsewhere in this issue for details). The target muscle representation then has a maximum value (optimal site), a center of gravity (CoG) (elements of the representation exceeding 50% of the maximum are used to form a weighted average of their location, in which the weights are given by the normalized value of the element), and a surface area (area where amplitude exceeds 50% of maximum). One of the advantages of this mapping technique is that the optimal site is determined by data from multiple sites, rather than selecting 1 site of largest response. This method has a resolution sufficient to distinguish the optimal site for 2 muscles within the same hand.[8]

Mapping performed with TMS can thus be used to reveal the size of the corticospinal representation of a particular muscle at a given stimulus intensity. As cortical representation

increases, the current depolarizes a greater number of cortical cells (in part because of increased current spread), resulting in a steeper curve. Changes in motor cortical maps are also reflected in changes in the slope of stimulus-response curves. Increased excitability of the corticospinal projection is evident from larger MEPs, resulting in a steeper slope of stimulus-response curves and greater area of the representational map.

TMS has developed into a technique that allows the closest noninvasive approximation to electrical cortical stimulation. There have been numerous general reviews of the technique and of the potential for TMS in studies and treatment in neurorehabilitation.[9] Although modeling TMS effects on the brain is an area of active research, the current standard approach is to examine simple maps of responses and determine the CoG and a metric of map size. The CoG is a useful metric because it gives each location stimulated a weight based on the size of the response there. Because the CoG is the result of so many data points, it has a low standard error and high degree of reproducibility. It can be determined with millimeter accuracy, but has no bearing on the spatial extent of the representation. For that purpose, the map volume is often used, which is a sum of the average MEP at each location stimulated, normalized to the average MEP at the location of the largest response. The map volume thus varies from 1, indicating a response at only 1 location, to N, where N is the number of locations in which any response is measured. Stimulation is generally performed at a fixed percentage of the motor threshold, the stimulus strength that elicits measurable MEP in at least half the stimulations.[10] Map volume can be a confusing term, because it refers to the volume of a contour graph constructed on the scalp surface, but represents the area in which stimulation evokes a response.

The area of the map is more difficult to interpret because the site of stimulation with TMS is considerably less focal than that excited via electrodes placed on the cortical surface. The area of a TMS map is therefore a function of both the area of the underlying corticospinal map and the distance from the coil that corticospinal neurons can be activated. One consequence of this situation is that the higher the intensity of the TMS stimulus, the larger the area of the MEP map. In addition, the higher the excitability of the cortical neurons, the easier it is to stimulate them at a distance from the coil. Again, the apparent area of the MEP map is larger than if excitability is low. Levels of excitability are particularly problematic in mapping studies that are performed in individuals who are at rest. The excitability of the corticospinal system in individuals at rest is ill defined: neurons can be quiescent because they are 1 mV from firing threshold or because they are 10 mV from threshold. In the former case, excitability is higher and the MEP map larger than in the latter. In addition to cortical excitability, the area of MEP maps also depends on the excitability of spinal mechanisms. Mapping of the patient typically takes place with the individual at rest, the coil placed tangentially on the scalp with the handle pointing backward and perpendicular to the central sulcus (Fig. 3). After determination of resting motor threshold of the small hand muscles, stimulation is performed at stimulation sites approximately 2 mm apart over an array centered on the central sulcus.

At times, the induced electrical charge after single-pulse TMS is often insufficient to disrupt cortical activity. Instead, repetitive TMS (rTMS) with fast repetition rates is necessary to map these functions. rTMS provides a new window into brain function by creating transient deficits in normal individuals. The higher the stimulation frequency and intensity, the greater is the disruption of cortical function during the train of stimulation. However, after such immediate effects during the TMS train itself, a train of repetitive stimulation can also induce a modulation of cortical excitability. This effect may range from inhibition to facilitation, depending on the stimulation variables (particularly frequency of stimulation).[11] Lower frequencies of rTMS, in the 1-Hz range, can suppress excitability of the motor

cortex,[11,12] whereas 20-Hz stimulation trains seem to lead to a temporary increase in cortical excitability.[12,13]

Advantages of nTMS

Recent advances in image processing have allowed the refinement of current TMS-mapping strategies by combining MRI modalities with TMS using a three-dimensional (3D) digitizer to measure the position of the stimulating coil and map this position onto an MRI data set. A frameless stereotactic system (FSS) that is rigidly fixated to the stimulating coil is used to correlate scalp stimulation sites to the underlying brain anatomy in real time (Fig. 4A). The anatomic accuracy as provided by MRI is combined thereby with the functional motor specificity provided by TMS to introduce stereotactic or nTMS as a new brain-mapping modality. The accuracy of this new technique has been validated by correlating nTMS maps to cortical output maps obtained with direct electrical cortical stimulation (DECS)[14] and to fMRI motor output maps.[15] In addition to the structure-function correlation of nTMS, this technique further allowed for integration of different brain-mapping methodologies by providing a common coordinate system for fMRI and DECS maps.

Coregistration of anatomic MRI data to the sites of stimulation during the TMS session is obtained with the aid of an FSS. This system consists of a jointed mechanical arm, functioning as a stereotactic 3D digitizer, and a computer workstation. Optical encoders in the arm continually measure the angular position of the arm and transmit this information to the computer-graphics workstation, where the spatial position of the tip of the arm is computed in real time and plotted on the MRI data set of the individual's head. The individual's head is spatially coregistered to the MRI by means of fiducial markers that are identified on both the MRI data set after imaging is completed and the head during the TMS session. From those 2 sets of coordinates, a matrix transformation is calculated that allows the computer to display the coordinates of the arm tip on the 3D MRI in real time.[16,17]

Recent studies have highlighted the usefulness of such real-time navigation in identifying cortical motor representation (see Fig. 4B). Säisänen and colleagues[18] showed that TMS readily identified the primary motor area when it was impossible to elucidate, from visual inspection alone, where the central region was located. The localization was confirmed via DECS during open brain surgery. The same study showed in another patient in whom both fMRI and nTMS were obtained preoperatively to identify the cortical representation of the tongue muscles, fMRI showed a large cortical region after motor activation of the tongue extending to postcentral areas, whereas nTMS exclusively identified precentral cortical regions. It was hypothesized that the postcentral areas identified by fMRI were caused by sensory coactivation during the performance of the task. This assumption was confirmed during open brain surgery, in which MEPs were elicited only from the precentral cortical areas as previously identified by nTMS.

INTEGRATION OF TMS WITH OTHER BRAIN-MAPPING TECHNIQUES

Neuroimaging techniques, commonly used to acquire functional cortical representation, such as fMRI, PET, EEG, or MEG, have limitations. fMRI and PET provide indirect measures of brain activity with low temporal resolution. EEG and MEG lack in spatial resolution. None of these methods can provide true insights into causal relations between brain activity and behavior. However, combining such neuroimaging and neurophysiologic methods with TMS offers unique advantages: (1) MRI or PET activation can guide where to stimulate and (2) real-time EEG recording can guide when to stimulate.

For example, Sack and colleagues[19] used neuronavigated TMS to quantify the interindividual variance in the exact location of human middle temporal complex (hMT/

V5+) and the respective TMS target position on the skull of the study participants. These investigators showed that targets for TMS application can be reliably selected by individual activation patterns from an fMRI experiment (Fig. 5). Area hMT/V5+ was identified in individual participants using a motion-mapping paradigm. Anatomic and fMRI data were coregistered with stereotaxic data from the participants' heads, and TMS was applied to the individually defined stimulation sites. TMS at hMT/V5+ but not at a parietal control site led to a significant reduction of correct motion discriminations in an early (−40 to −30 ms) and a late (130–150 ms) time window. In such paradigms, using individual neuronavigation proves to be an important methodological improvement because, first, the exact location of hMT/V5+ can vary considerably between participants and, second, moving phosphenes, which are used to identify hMT/V5+ functionally, can be produced only in a small percentage of participants.[20] Such a methodological approach enables us to reveal and quantify the interindividual variance in the exact location of the target cortex and the respective TMS target position on the skull of the participants.

Since epileptiform spikes were shown in epileptics by Fisher and Lowenback in 1934, the use of EEG in a clinical setting has grown to include other areas such as sleep disorders, strokes, infectious diseases, brain tumors, mental retardation, severe head injury, drug overdose, and brain death.[21] EEG is especially useful in exploring the virtual lesions caused by TMS (areas where normal operation is disrupted), which are not limited to the stimulated spot but distributed along the neuronal network.[22,23] Furthermore, a growing number of studies indicate that the effects of TMS depend on the state of neuronal activation in the targeted brain region at time of stimulation.[3,22,23] Thus it is conceivable that individual EEG, which is carrying useful information to infer momentary brain state across time and participants, can be used for tailoring TMS effects by fine-tuning the time of stimulation (Fig. 6). The notion of EEG-gated TMS to maximize therapeutic efficacy is appealing; however, future studies of TMS coupled with real-time EEG (TMS-EEG) are needed to address this point.

On the other hand, although fMRI has revealed much about the processing in the human brain, it can provide insight only into the brain areas associated with a given behavior, failing to establish a causal relation between brain activity and behavior. To bridge the gap between association and causality it is necessary to disrupt the activity and assess the effect on behavior. fMRI cannot tell the neurosurgeon that lesioning a given brain region, whether it shows activation during a task or not, will cause a postsurgical deficit. The combination of fMRI with TMS can provide such insight.[24]

CLINICAL APPLICATIONS OF TMS MAPPING

Over the last 2 decades, several studies have used TMS mapping in a wide range of experimental conditions. In addition to providing insights into the state of cortical representation in healthy individuals, TMS mapping has been used in studying the evolution of various pathologic conditions. Some of the most relevant neurosurgical uses of TMS mapping have been in patients with brain tumors, cerebral palsy, epilepsy, and stroke.

Tumor Mapping

Motor mapping—DECS is considered the gold standard for functional mapping of the motor cortex; however, for the planning of surgical approaches and procedures, preoperative functional maps of the motor cortex are required as well. Furthermore, in some cases the ability to precisely locate functional areas can become a determinant for feasibility of the neurosurgical intervention. Traditionally, most of the perioperative functional analysis has been dependent on recording regional differences in metabolic or electric activity during patient movement by means of fMRI, PET, MEG, and EEG. Although fMRI in particular

has found widespread use in the preoperative planning, recent evidence points out the shortcomings of this technique because of the pathologic vessel architecture and the space-consuming effect in the tumor area, which make the interpretation of the fMRI data difficult.[25-27] Moreover, it remains unclear whether or not the activated areas are essential for the function.

More recently nTMS has been used for the functional mapping of the motor cortex in multiple studies[28-31] and has shown analogous functional testing to direct current stimulation (DCS) (Fig. 7). Although a spatial resolution of 5 mm is reported with TMS,[29,32] and spatial resolution may be even better with newer navigated systems, doubt regarding the spatioanatomic resolution of TMS remains, mainly because activation of the corticospinal tract is, in part, mediated transsynaptically through cortical interneurons.[33] Table 1 summarizes the major studies using TMS mapping as a perisurgical functional assessment tool. Data suggest strong correlation between the maps obtained through TMS and DCS (see Table 1), by showing that the specification of the position of the tumor in relation to the central sulcus is consistent between the 2 modalities. TMS is found to be useful not only in the preoperative functional mapping of the motor strip but also in the preoperative planning of the operative approach and intra-operative planning of the direction of brain retraction and operative corridor.

Mapping of language areas—Tumors located in the proximity of the language areas represent a special challenge for neurosurgeons. Involvement of the language functions with defined anatomic structures is not enough for the preservation of speech, because of variability of the cortical organization and distortion of the brain convolutions and fibers as a consequence of the mass effect of the tumor, as well as the functional reorganization related to neuroplasticity in the adaptation to the insult.[39-41] Of the various methods used to study language areas, DCS remains the most accurate method but as with other tumor resection procedures, it is associated with prolonged operative time, awake craniotomy, and discomfort for the patients. Conventionally, the intracarotid amobarbital procedure, more commonly known as the Wada test, has been used in the assessment of language lateralization; however, this test has major shortcomings because of its invasiveness, lack of standardization, absence of spatial resolution, and difficulties related to its application and interpretation.[42-44] In addition to the use of TMS in investigations of the motor system, high-frequency rTMS (20 Hz), which can cause transient deficits, has been used in the determination of the lateralization of motor speech with high concordance to the Wada test.[45,46] Tokimura and colleagues[47] have suggested an alternative approach to identify the dominant hemisphere with single-pulse TMS to measure the increase in motor-cortical excitability of the dominant (but not of the nondominant) hemisphere during language tasks. In any case, the correlation of TMS results with those of the Wada test is high but not fully satisfactory for a complete presurgical assessment.[46,48] However, Shamov and colleagues[31] have recently reported that using TMS for presurgical planning, the operative time was reduced from an average of 7 hours (using DCS) to an average time of 3 hours and 40 minutes (using TMS) in patients with opercular tumors with a volume more than 50 cm^3. The usefulness of TMS in such cases is augmented by the fact that studies looking at the use of fMRI for functional mapping of the language areas have shown discrepancies between DCS and fMRI results. For example, Giussani and colleagues[49] report the contradictory results when speech zone was mapped using DCS in comparison with fMRI mapping. This data inconsistency could be because DCS suppresses the projection fibers, whereas fMRI depicts the increased deoxygenated hemoglobin in the areas with an increased metabolic activity.

Beyond cortical mapping: promoting presurgical plasticity to optimize surgical outcomes—Repeated surgery of low-grade gliomas with DCS and serial fMRI

studies have shown that the cortical location of certain eloquent functions can be displaced as a consequence of the tumor growth.[50,51] This situation occurs when the tumor grows slowly (compared with a quicker onset of symptoms as in high-grade gliomas)[50] and apparently there is not a predictable pattern of reorganization.[52] A great advantage for increasing the extent of tumor resection would occur if we could artificially promote the displacement of eloquent functions in a quicker and more ordered way away from the vicinity of tumors. For example, it can thus be hypothesized that using high-frequency TMS, thetaburst stimulation, it might be possible to promote reorganization by disrupting the activity of the Broca area. Such reorganization might lead to compensatory changes away from the peritumoral area, which could minimize the postoperative deficit. Barcia and colleagues[53] have recently reported a case of 59-year-old woman operated for a left-sided precentral oligodendroglioma, which affected language areas. The patient was submitted to rTMS directed to the Broca area, next to the anterior pole of the tumor, with the aim of provoking a relay of potentially ancillary motor language areas that could justify a complete tumor removal. Twelve daily sessions of thetaburst rTMS followed by intensive language rehabilitation were performed. Although the initial expectation of anatomic displacement of the Broca area was not met, the experiment data showed modification in the language motor function, especially in repetition and denomination. The investigators concluded that this effect of rTMS could be potentially used to displace the topographic location of language cortical representation. Further studies seem warranted to examine the potential feasibility of such an approach to promote plasticity as a strategy to minimize postsurgical disability and maximize surgical resection.

Epilepsy

Functional mapping before respective epilepsy surgery—Patients with epilepsy who are candidates for resective surgery and whose seizure focus lies close to the eloquent cortex require accurate preoperative functional mapping of the epileptogenic zone and the surrounding area. The standard of care for preoperative functional localization is DCS via subdural electrodes. In this setting, preoperative functional mapping using nTMS can noninvasively localize the sensorimotor cortex and can determine its spatial relationship to the seizure focus.

Detailed preoperative nTMS mapping is particularly well founded when the epileptogenic focus is located near the sensorimotor cortex, and in instances in which cortical malformation might have altered the anatomic organization of the motor representation. In support of this approach, Vitikainen and colleagues[36] used nTMS mapping in epilepsy patients who subsequently underwent a week-long intracranial recording evaluation via subdural electrodes and resective surgery. These investigators showed that nTMS produced spatially more precise mapping of the motor cortical representations than subdural electrode DCS, and proposed that nTMS mapping should be added to the standard preoperative workup. Given that some morbidity and substantial financial cost are associated with any length of time that subdural electrodes are implanted, nTMS preoperative mapping may translate to improved efficiency of the epilepsy workup before respective surgery.

TMS in spike provocation—TMS-EEG has potential as a neurologic stressor to provoke epileptiform activity in a vulnerable cortical region. The usefulness of such TMS application in general may be to identify patients with lowered seizure threshold, but particularly with nTMS, a plausible application may be to enhance seizure focus mapping. Epileptiform discharge provocation by TMS has been shown in patients with epilepsy, but early results suggested that TMS was no more likely than hyperventilation to activate a seizure focus.[54-56] However, more recently, Valentin and colleagues[57] applied single-pulse TMS-EEG to patients with focal epilepsy and to a group of healthy controls. The investigators

identified 2 broad categories of electrographic-evoked response: an early (<100 millisecond) slow-wave response and a late (100–1000 millisecond) response, which was either epileptiform in morphology (resembling a sharp wave or spike) or was characterized by rhythmical EEG activity. Although the early responses were present in all patients, the late epileptiform responses were detected only in patients with complex partial seizures. These late discharges often appeared similar to the patients' habitual spikes or sharp waves and were lateralized to the epileptogenic hemisphere in most cases. Moreover, in some instances in which epileptiform abnormalities were triggered by TMS, the interictal scalp EEG was normal.[57] As Valentin and colleagues propose, these data raise the prospects for eventual applications of TMS-EEG to enhance the sensitivity of the scalp EEG in detecting epileptiform abnormalities. Whether and to what extent nTMS can enhance the spatial resolution of seizure focus localization is the work of ongoing experiments. However, if sufficiently sensitive and specific, nTMS seizure focus localization, like nTMS presurgical functional mapping, may translate to a reduced number of subdural electrodes and a shorter invasive recording time, and thus reduced morbidity and economic cost.

Beyond cortical mapping: modulating cortical excitability with therapeutic intent—A further conceivable application of TMS in evaluation of epilepsy is its potential to reduce cortical excitability and by this means raise the seizure threshold. The mechanisms that underlie therapeutic effects of rTMS are not entirely known, but seem to resemble those of long-term depression and long-term potentiation of synaptic strength that result from low- or high-frequency electrical brain stimulation, respectively.[58,59] In epilepsy, the inhibitory effect of low (≤1 Hz) rTMS is most widely used to suppress seizures, with encouraging antiepileptic results in open-label trials.[60-62] Yet, results from placebo-controlled trials are mixed, with 1 trial reporting a reduction in seizures and improvement of the EEG,[63] and 2 others reporting insignificant clinical improvement, or improvement of the EEG without a significant reduction of seizures.[64,65] Similarly, results from open-label rTMS applications in ongoing seizures of epilepsia partialis continua are mixed with some instances of seizure termination after rTMS, and other instances of continued seizures despite stimulation.[66]

The partial efficacy of rTMS in seizure suppression may relate to suboptimal targeting of the seizure focus. Here, nTMS may be useful in targeting more precisely a radiographically apparent seizure focus such as a tumor or a cortical dysplasia.

Stroke

Functional mapping in poststroke recovery—The molecular and cellular changes after stroke are reflected by a significant reorganization of the postlesion motor cortical map. The pattern of the postlesion map depends on the initial lesion size and on its precise position in the brain. Frost and colleagues[67] showed that the smaller the damage to M1, the less compensatory reorganization was seen in the ventral premotor cortex (PMv). An animal model has shown that destroying 33% of the M1 hand area does not promote observable changes in PMv, as seen with larger lesions.[68] As a consequence of that finding, reorganization of motor cortical maps induced by small M1 lesions is not necessarily easy to detect by custom stimulation/imaging techniques outside the core of the lesion. Nevertheless, many postlesion stimulation studies with ICMS (monkeys, rats) or TMS (humans) have provided insight into motor cortical reorganization. Such insights prove invaluable for surgical planning in patients who have undergone such reorganization after stroke.

TMS mapping provides dual insight in tracking recovery after stroke. In addition to providing information about the processes arising naturally during stroke recovery, it also allows for the investigation of poststroke brain plasticity that may result from therapeutic

interventions. For example, studies have shown that the arm- or hand-muscle MEP amplitudes measured soon after a stroke can predict the degree of behavioral recovery weeks to months later.[69-73] Others suggest that stroke alters intracortical excitability[73] (as measured by the paired-pulse TMS paradigms) and successful recovery is associated with normalization of these measures.[74] Moreover, rTMS can be used to determine whether a particular region participates in a recovered function by assessing whether focal stimulation of that region alters behavior.[12,75]

Beyond cortical mapping: modulating cortical excitability with therapeutic intent—TMS can also be used to modulate cortical excitability and corticocortical and corticosubcortical connectivity with therapeutic intent. For example, there is increasing evidence that during voluntary movement generation after stroke, the interhemispheric inhibitory drive from the unaffected to the affected motor cortex is abnormal.[76] Acutely after a stroke, increased inhibitory input from the healthy to the lesioned hemisphere may develop as the neural attempt to control perilesional activity. However, after the acute phase we might expect a shift of interhemispheric interactions from inhibitory to excitatory to maximize the capability of the preserved neurons in the injured tissue to drive behavioral output. Should such a shift fail to take place, the resulting functional outcome may be undesirable, with limited behavioral restoration, in part because of persistent inhibitory inputs from the healthy to the injured hemisphere. Some neuroimaging studies show that long-term, persistent activation of the ipsilateral cortex during motor tasks is associated with poor motor outcomes, whereas a good motor recovery is associated with a decrease in activity of the unaffected motor cortex, and an increase in the affected primary sensorimotor cortex activity.[77,78] Leveraging this information, one can conceive that suppression of the ipsilateral motor cortex through low-frequency (inhibitory) rTMS may enhance motor performance in patients who have stabilized after the acute phase of stroke. Mansur and colleagues[79] showed that in patients 1 to 2 months after a stroke, 0.5 Hz rTMS for 10 minutes to the unaffected hemisphere can suppress cortical activity and release the damaged hemisphere from potentially excessive trans-collosal inhibition. Longitudinal studies with larger samples of patients after a stroke and correlation of interhemispheric interactions with functional measures are needed to further explore these avenues.

Other Clinical Applications of TMS Mapping

Chronic pain—The principle of mapping the cortex to gain insight into cortical reorganization can be applied to other clinical conditions as well. In chronic neuropathic pain, studies have shown a reduction of intracortical inhibition in the contralateral hemisphere. This disinhibition has been shown to be more pronounced in patients with moderate/severe pain intensity than in patients with mild pain intensity.[80,81] Krause and colleagues[82] have shown that in patients with complex regional pain syndrome, the cortical representation (size, MEP, and calculated volumes) is significantly larger for the unaffected hand than for the affected hand. Furthermore, in patients with low-back pain, TMS mapping has provided preliminary evidence of reorganization of trunk-muscle representation at the motor cortex and suggest that this reorganization is associated with deficits in postural control.[83]

The motor cortex has extensive projections to some thalamic nuclei (which along with the somatosensory cortex and the limbic system are considered critical in the pathophysiology of chronic pain).[84] Converging evidence suggests that modulation of the motor cortex may be beneficial in chronic pain.[80] The primary motor cortex might represent a convenient portal for the modulation of deep brain structures with difficult access: the motor cortex stimulation triggers corticothalamic output to brainstem, spinal cord, and also limbic system, exerting an inhibitory effect on these pathways. Several studies, using rTMS and

transcranial DCS for therapeutic modulation, have been conducted in this area and significant results have been shown.[85] Moreover, treatment of chronic visceral pain with brain stimulation is also being explored, with promising preliminary results.[86]

PD—TMS-mapping studies of patients with PD have shown altered cortical physiology in basal-ganglia-connected areas such as the supplementary motor area, dorsolateral prefrontal cortex, and primary motor cortex, characterized by excessive corticospinal output at rest and reduced intracortical inhibition.[87,88] Because a given motor task is associated with suppression of competing motor networks, these cortical changes in patients with PD might result in decreased suppression and therefore decrease the performance of the motor system, resulting in symptoms such as tonic contractions and rigidity.[87]

Although the motor symptoms of PD are mainly treated with drugs, the clinical usefulness of these medications tends to become limited over the years, often because of adverse effects such as dyskinesias. Nonpharmacologic approaches, such as deep brain stimulation (DBS), are effective in the treatment of PD motor symptoms in selected patients. Recent developments in DBS have reduced surgical risks and morbidity, but noninvasive approaches are still appealing. rTMS has been used in patients with PD to modulate activity in specific neural networks, using cortical targets as entry ports. Two pathophysiologic mechanisms can be proposed to explain how cortically directed rTMS may improve PD symptoms: either (1) rTMS induces network changes that connect with and positively affect basal-ganglia function[89,90] or (2) rTMS to cortical sites compensates for systematic abnormal changes in cortical function associated with PD.[91-93] Although these mechanisms of action are based on several studies that have attempted to elucidate the pathophysiology of motor disturbance in PD, they remain unproved, and further investigations are required.

SAFETY CONSIDERATIONS FOR TMS MAPPING

Single-pulse stimulation within current guidelines poses low risk of adverse effects in healthy individuals and patients.[94] TMS has been safely used in both children and adults for the explicit purpose of presurgical mapping.[18,28-31] The most severe adverse effect is considered nonintentional seizure after rTMS. From the several thousands of studies that have used TMS, 16 such cases have been reported. Based on the available data, the reported risk of seizures is less than 1 in 1000 for rTMS.[94] Because TMS can have lasting effects on cortical excitability depending on the stimulation parameters (largely frequency and intensity), the seizure risk is related to how the stimulation is applied. High-frequency stimulation can raise cortical excitability and may be unsafe if performed outside the safety guidelines, whereas low-frequency stimulation can reduce cortical excitability.[95] However, the seizure risk is considered minimal with single-pulse stimulation, which is most frequently used for presurgical mapping. The intensity typically use for mapping is 120% of the resting motor threshold, but in some patient groups, in which no response can be elicited at this intensity, up to 100% maximal stimulator output has been reported.[96] Operators should be aware that sedation and anesthesia might raise cortical excitability. With increasingly more powerful coils and stimulators emerging, one should take care to gradually increase the stimulus intensity in a stepwise fashion (see safety guidelines).[94]

In some cases, depending on the stimulus intensity and current spread from TMS, mapping can exceed the anatomic primary motor area and border nonmotor areas; because the stimulus intensity selected remains relative to the motor threshold, stimulating nonmotor areas at this intensity is not considered harmful.[94]

Physiologic monitoring should minimally involve visual inspection that the muscle twitch from TMS remains limited to the associated body part and seems to immediately follow the

stimulus. A more quantitative method may be to additionally record EMG from higher threshold or more proximal muscles represented outside the region to be evaluated. If single-pulse TMS over the region of interest begins to elicit responses in this second EMG channel, this would be an indication of increased cortical excitability, and possible spread of intracortical excitation. EEG monitoring is routinely used as a safety feature in intracranial cortical stimulation and could be used during TMS mapping, yet provides equivocal additional benefit.[94]

Based on the ex vivo and in vivo studies, it is suggested 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 system.[94] However, detailed information as to what constitutes a safe distance between the TMS coil and the implanted stimulator is still lacking. Therefore, TMS should only be performed in patients with implanted stimulators if there are medically compelling reasons justifying it.[94] Furthermore, recent data show the absence of adverse events related to titanium (Ti) skull plates in patients undergoing 1-Hz rTMS.[97] These initial data showed that Ti skull plates, even if positioned directly beneath the TMS coil, were minimally heated and unlikely to be displaced by a conventional low-frequency rTMS protocol. However, more data are required to conclude that rTMS in patients with Ti skull plates is definitively minimal risk.

SUMMARY

The notion of remapping has led to significant advances in how we understand the multifactorial process of recovery after injury of the central nervous system. There are experience-dependent processes that likely involve disinhibition of previously inhibited connections as well as stabilization of new synapses. However, the map metaphor has also led to an exaggerated conception of postlesion plasticity. For example, the map expansion found by TMS that seems to be related to therapy may come about through changes in inhibition, excitability, and potentially spinal cord circuitry, and therefore may not represent the same kind of remapping as found in experimental motor cortical lesions. Although such cortical maps need to be reviewed in conjunction with clinical and other diagnostic evidence, they provide us with an important set of electrophysiologic information both for a healthy brain, and for cortical reorganization after lesion.

The presurgical usefulness of nTMS depends mainly on the spatial resolution and the application error of the method by which TMS is used. With the development of newer and more focal nTMS systems, the resolution of the stimulation maps can be further enhanced, by moving the coil in small increments and stimulating just over the threshold with a controlled and monitored level of muscle contraction. Using such meticulous mapping protocols, TMS can prove to be an indispensable tool to study cortical connections in humans noninvasively and painlessly. Moreover, integration of TMS with functional neuroimaging can add to both the spatial and temporal resolution of the mapping strategies.

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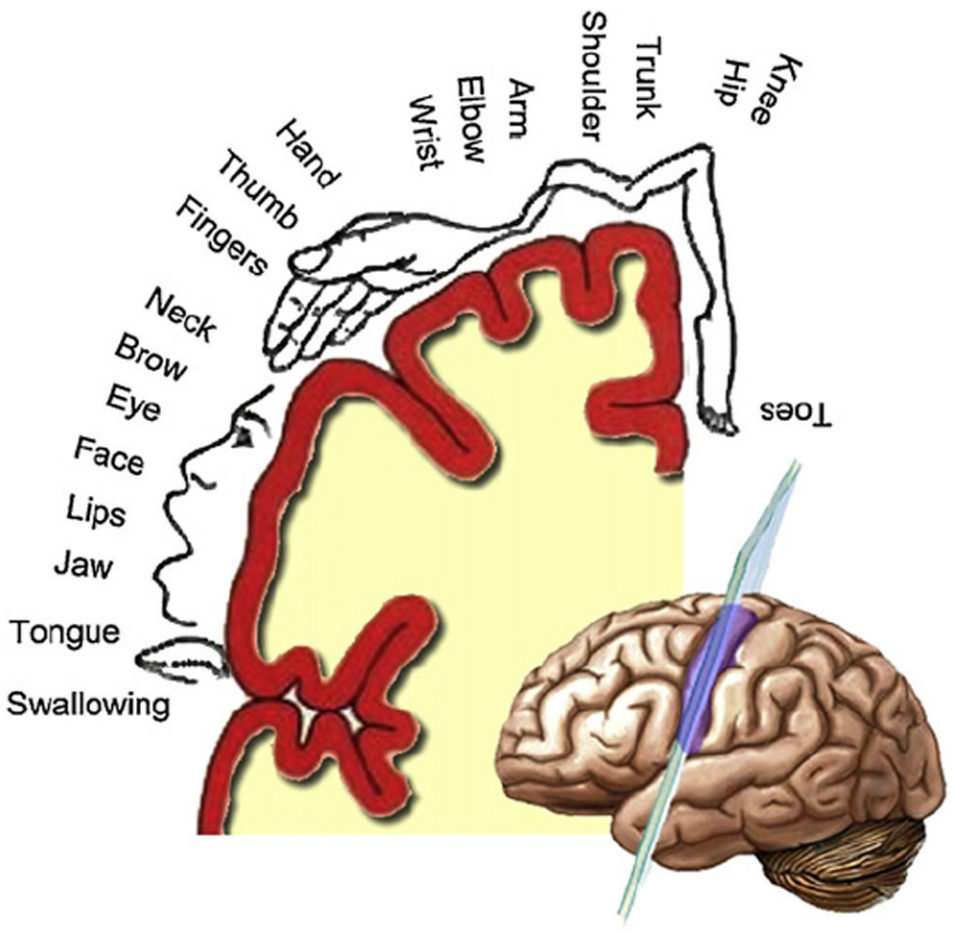

Fig. 1.
The homunculus as described by Penfield and Rasmussen. (*Adapted from* Penfield W, Rasmussen T. The cerebral cortex of man. New York: Macmillan; 1950. p. 44, 56, 214–5.)

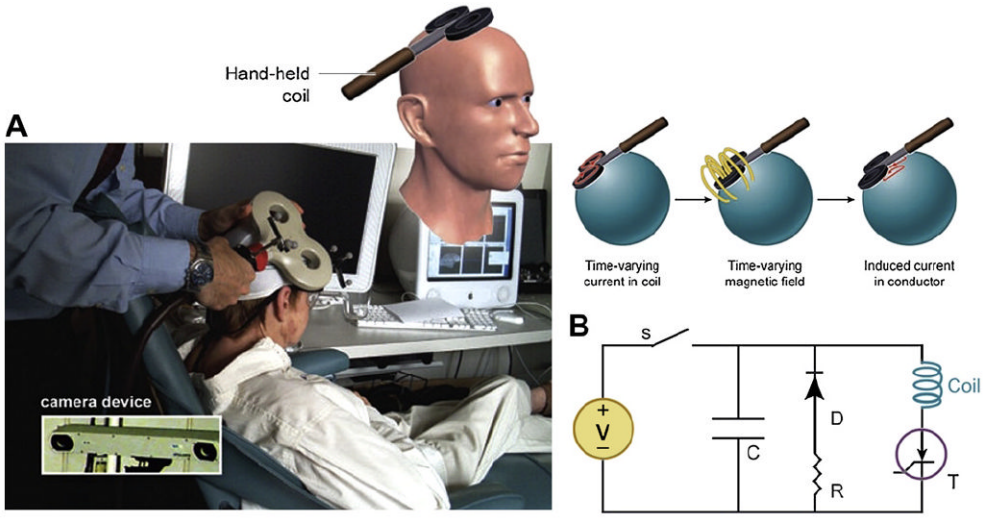

Fig. 2.

(*A*) During TMS, a time-pulsed current is discharged through the TMS coil. The resulting time-varying magnetic field is focused onto underlying neural tissue. The eddying currents, produced in the tissue, can affect the neural activity during and after stimulation. The patient is shown wearing a frameless stereotactic device that can be used to predict the location of stimulation relative to the TMS coil, which is tracked via the camera device (*inset*). (*B*) A simplified circuit diagram of a single-pulse magnetic stimulator. C, capacitator; D, diode; R, resistor; s, switch; T, thyristor; V, voltage source.

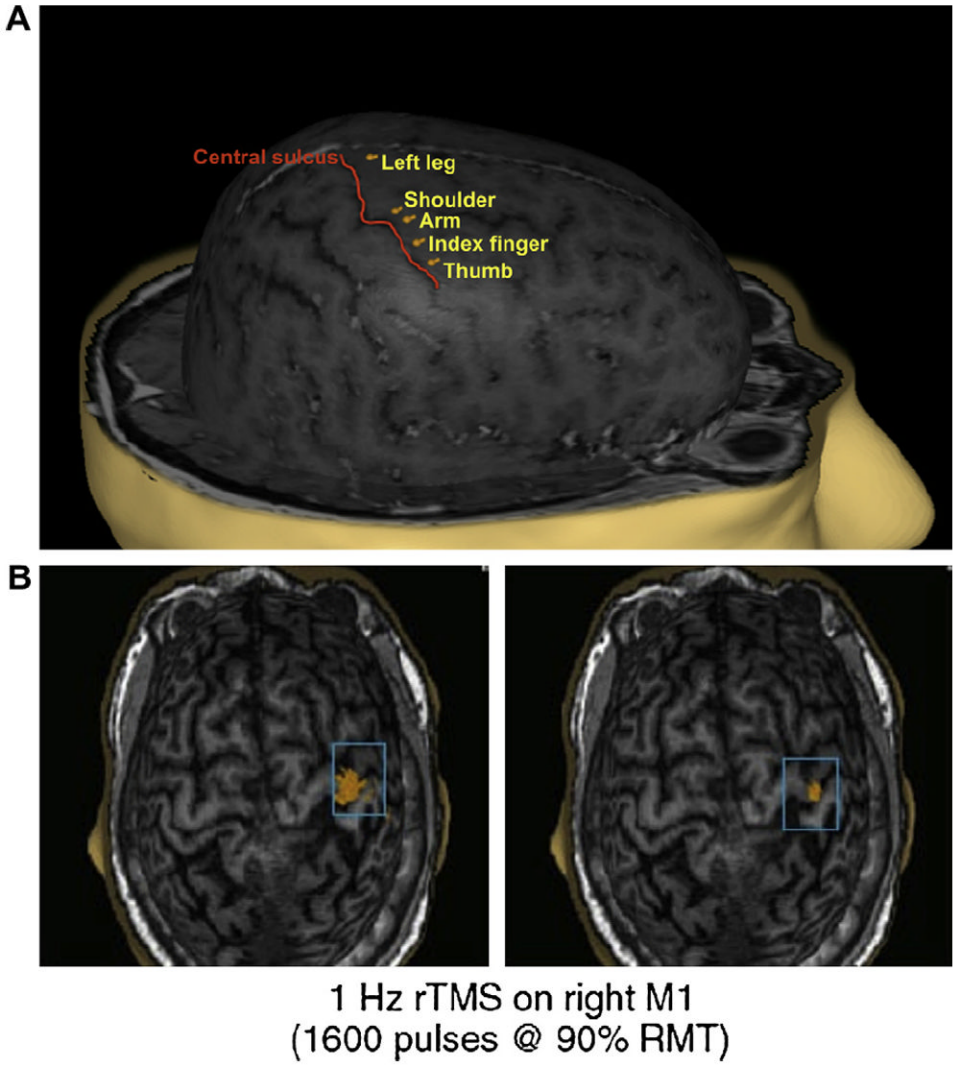

Fig. 3.

(*A*) Head model showing right M1 mapping performed in a healthy individual for upper and lower limb. Each mark represents the hot spot for the muscle mapped. The position of the head of the mark represents the direction of stimulation. The brain is peeled to a depth of 25 mm (ie, the visualized stimulation surface resides at this depth from the scalp). (*B*) Comparison between navigated (*right*) and nonnavigated (*left*) stimulation (1 Hz rTMS) performed in the same individual, on the same target. Note that in the navigated intervention, the dispersion of the stimuli is less and it is more focal than the nonnavigated intervention.

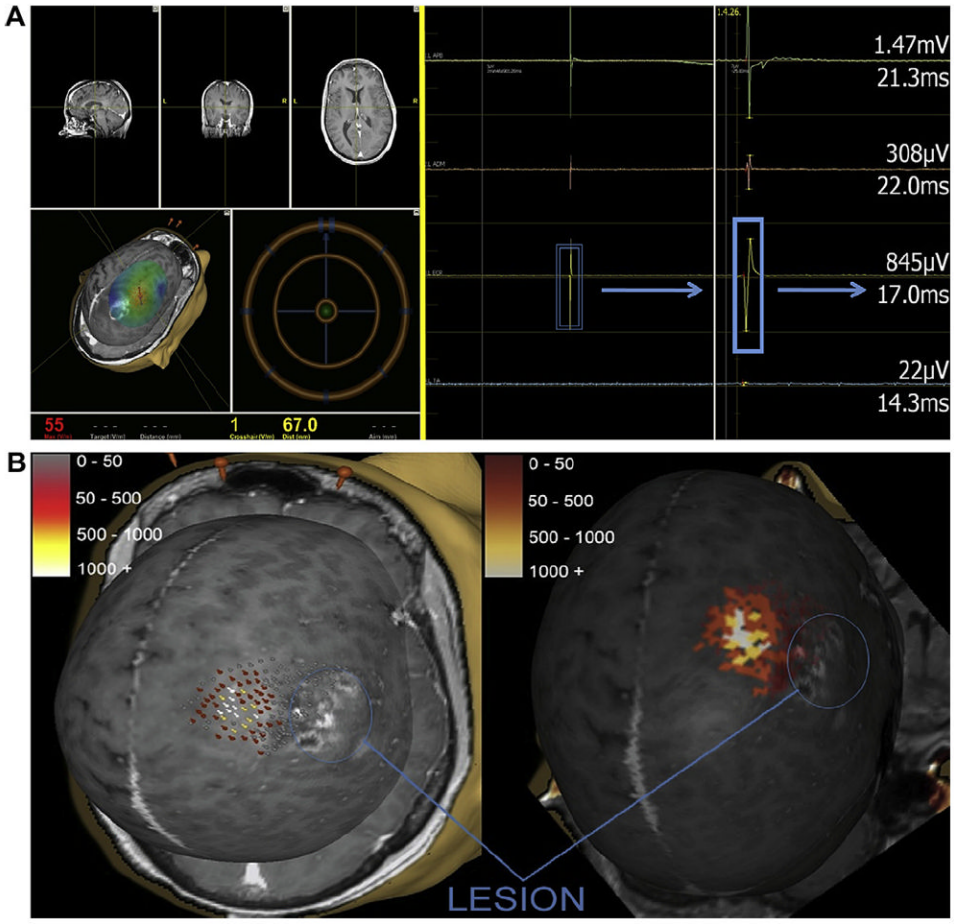

Fig. 4.

(*A*) An nTMS system user interface. (*Left panel*) The interface allows the user to identify and select stimulation targets based on the patient's anatomic or functional imaging. It also generates a 3D head model (*bottom left*) for accurate estimation of the target electric field strength. The targeting system (*bottom right*) allows the user to stimulate with enhanced spatial resolution. The position feedback indicator provides real-time feedback surface location, roll, pitch, and yaw of the coil, for consistent and reliable targeting. (*Right panel*) Online EMG recording, along with a modifiable epoch view (*right half*). A single evoked response is measured as peak-to-peak amplitude and onset latency. ADM, abductor digiti minimi; APB, abductor pollicis brevis; ECR, extensor carpi radialis. (*B*) Presurgical cortical maps produced in a patient with right parietal lesion. EMG amplitude-based map on the left side can be viewed only in the navigated brain stimulation system. Amplitude-weighted maps on the right side can be viewed in any third-party imaging system capable of reading DICOM (digital imaging and communications in medicine) images.

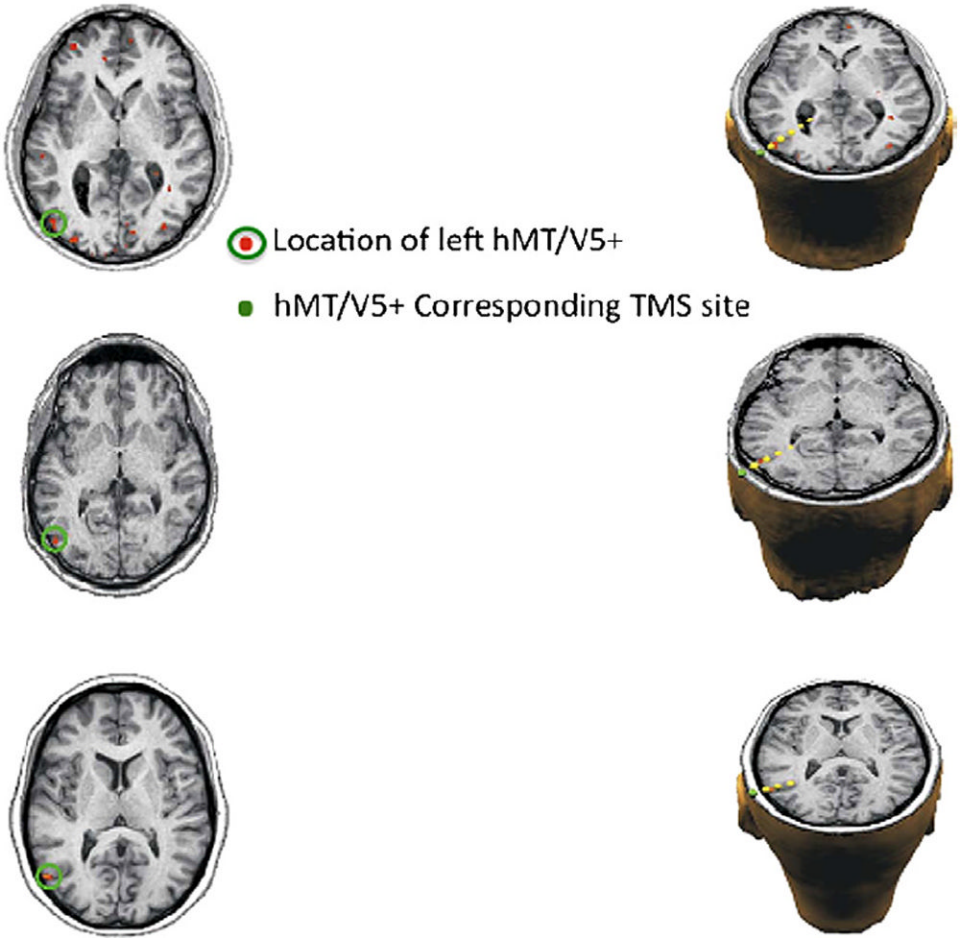

Fig. 5.

Axial slices through head reconstructions showing the hMT/V5+ stimulation site (*green sphere*) relative to motion-specific activation, representing the location of hMT/V51 (*red sphere*; calculated using a motion-mapping paradigm; for details see text). The yellow spheres visualize the orientation of the TMS coil. The imagined line through the spheres corresponds to the normal vector originating from the TMS focus (distance between spheres is 1 cm). (*Data from* Sack AT, Kohler A, Linden DE, et al. The temporal characteristics of motion processing in hMT/V5+: combining fMRI and neuronavigated TMS. Neuroimage 2006;29(4):1326–35.)

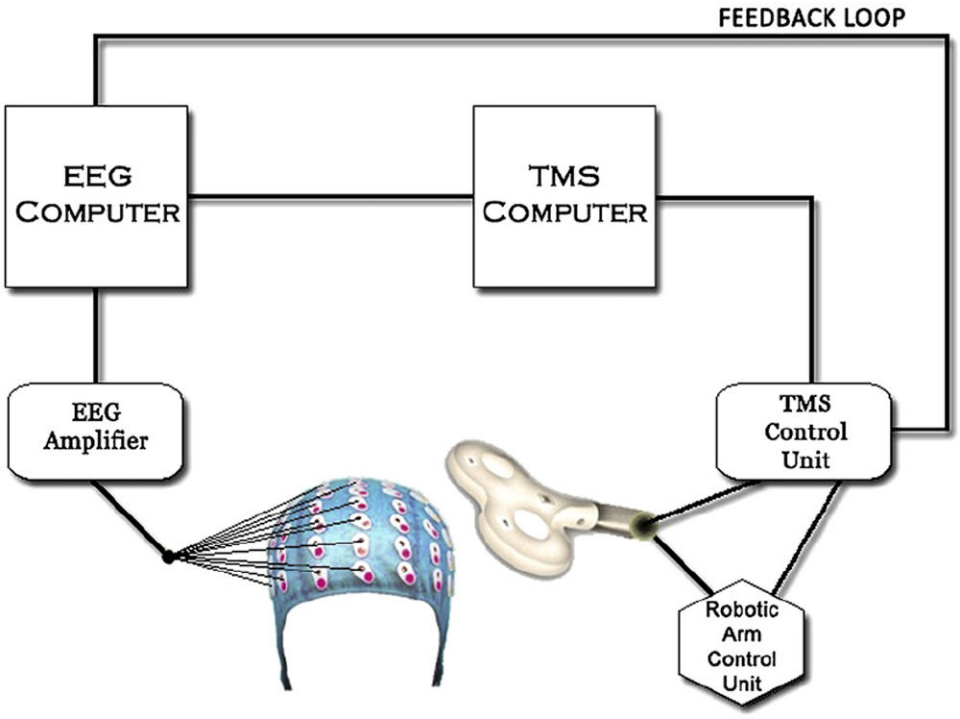

Fig. 6.

A combined TMS-EEG system. Note that in addition to triggering TMS using criteria based on online EEG recording (such as a specific event-related potential), TMS triggering can be used to control EEG recording as well (such as momentary stoppage of EEG recording immediately after a TMS pulse to prevent saturation of EEG amplifiers because of excessive voltages induced between the leads because of the magnetic field).

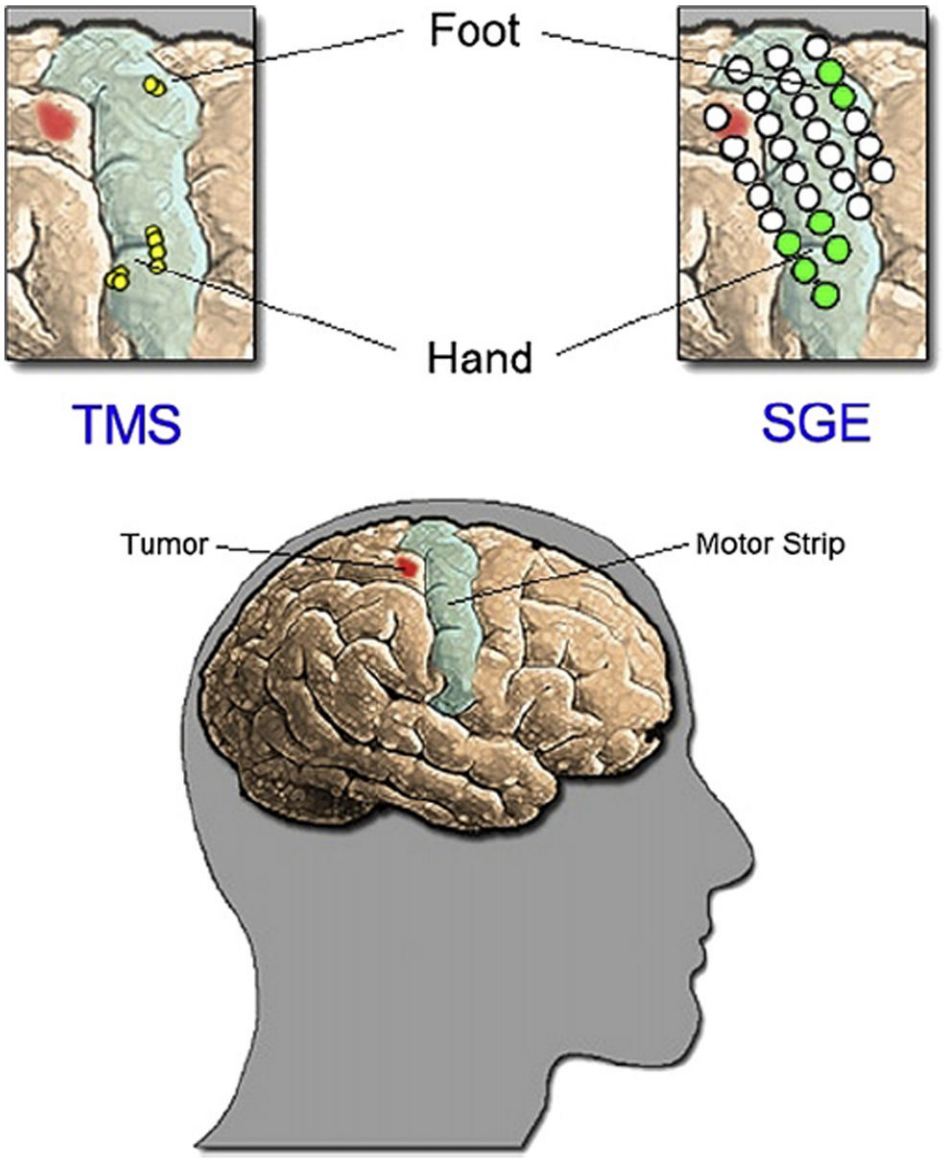

Fig.7.

Head-model recreationofa comparisonbetween navigated brain stimulation (*left*) and direct cortical stimulation (*right*) in a patient with right parietal tumor. Yellow marks on the TMS panel represent the hot spots for hand and lower-limb muscles. Green dots on the SGE grid represent points that resulted in responses from hand and lower limb. SGE, subdural grid electrodes.

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Table 1

Major studies using TMS mapping as a perisurgical functional assessment tool

Studies	Techniques Used for Cortical Mapping	Areas Mapped	n	Diagnoses	Side Effects of Mapping	Surgical Implications and Insights
Focal Lesions						
Krings et al,[29] 1997	nTMS MRI DCS	M1 (tongue and hand area) Left hemisphere	2	1 oligodendroglioma 1 mixed astrocytoma and oligodendroglioma	None reported	TMS mapping helpful in surgical planning One patient had temporary word-finding difficulty for several days Distance between optimal point determined via TMS and DCS = 2.5 mm (average); 0–4.7 mm (range)
Krings et al,[1] 2001	nTMS MRI fMRI	M1	10	–	None reported	TMS mapping helpful in surgical planning No major postoperative complications reported Distance between optimal point determined via TMS and fMRI = 0.6 cm (average); 0–1.2 cm (range)
Picht et al,[30] 2009	nTMS MRI DCS	M1 (hand area) Bilateral	10	3 gliomas 1 meningioma 3 glioblastma 3 metastasis	None reported	TMS mapping helpful in surgical planning No major postoperative complications reported Distance between optimal point determined via TMS and DCS = 3.4 mm (average); 0–7 mm (range)
Juenger et al,[34] 2009	nTMS MRI MEG fMRI DCS SEP	M1 (hand area) Bilateral	1	AVM	None reported	TMS mapping helpful in surgical planning No major postoperative complications reported
Shamov et al,[31] 2010	rTMS MRI CT	Opercular area Left hemisphere	5	5 gliomas	None reported	TMS mapping helpful in surgical planning 3 patients had transient postoperative motor aphasia, which resolved within 1 month Mean operative time reduced from 7 h (without TMS) to 3 h 40 min (for tumors >50 cm^3) with TMS
Kantelhardt et al,[28] 2010	R-nTMS MRI fMRI DCS	M1 (hand area) Bilateral	5	1 meningioma (grade 1) 1 astrocytoma (grade 2) 1 astrocytoma (grade 3) 2 glioblastomas (grade 4)	Focal seizure in 1 patient: mapping discontinued	TMS mapping helpful in surgical planning No major postoperative complications Distance between optimal point determined via TMS and DCS <5 mm (1 patient) Preresection DCS not performed in the rest
Epilepsy						
Rutten et al,[35] 2002	nTMS MRI fMRI	M1 (hand area) Bilateral	1	Left hemispheric stroke resulting in epilepsy/cortical atrophy	None reported	TMS mapping helpful in surgical planning No major postoperative complications reported
Kamida et al,[98] 2003	TMS MRI DCS SEPs	M1 Bilateral	5	Intractable epilepsy and hemiplegia	None reported	TMS mapping helpful in surgical planning No major postoperative complications reported

Studies	Techniques Used for Cortical Mapping	Areas Mapped	n	Diagnoses	Side Effects of Mapping	Surgical Implications and Insights
Vitikainen et al,[36] 2009	nTMS MRI fMRI DCS	M1 Bilateral	2	Intractable epilepsy	None reported	TMS mapping helpful in surgical planning No major postoperative complications reported
Barba et al,[37] 2010	TMS fMRI SEPs	M1 Bilateral	1	Intractable epilepsy and left perisylvian polymicrogyria	None reported	TMS helpful in defining the relationship between epileptogenic zones and somatomotor areas Surgery not performed because multimodal assessment suggested that removal of the polymicrogyric cortex would have caused severe deficits
Schmidt et al[38] 2010	nTMS MRI	M1 Bilateral	1	Intractable epilepsy, somatosensory auras, and epilepsia partialis continua	None reported	TMS mapping helpful in surgical planning No major postoperative complications reported

Abbreviations: AVM, arteriovenous malformation; CT, computed tomography; R-nTMS, robot assisted nTMS; SEP, somatosensory evoked potential.