Functional lesions of the motor system with TMS – a challenge for individual functional mapping

M. Lotze*

Functional Imaging; Institute for Diagnostic Radiology and Neuroradiology, University of Greifswald, Germany

Abstract. Applying functional lesions using functional magnetic resonance imaging (fMRI)-navigated transcranial magnetic stimulation (TMS) is a powerful method for investigation of the functional relevance of a given activation site for motor performance in healthy individuals, and also for investigation of the temporal interactions of particular areas during movement preparation. In patients with good cognitive compliance, this procedure may be useful for detection of functional reorganisation or to plan individual therapy directions. Different protocols for applying functional lesions are presented here and their relevance and usage in different applications are explained.

1. Introduction

Functional imaging has a major disadvantage: comparisons must be performed at the group level to discover relevant mechanisms for rehabilitation, for example, with regard to lesion location (Luft et al., 2004) or other clinical issues. This type of imaging allows clinicians to recognise general mechanisms that may vary remarkably between individuals or between patients in the same clinical group. In contrast, single-subject fMRI-investigations are often highly variant in time (Neumann et al., 2003), and the statistical threshold used cannot help us decide whether a certain region is involved in a functional process. This is a significant problem for precise presurgical planning using functional MRI. On a methodological level, BOLD-response only provides data on a correlational basis and cannot be used for deciding whether a certain region is functionally relevant for performing a certain task. In

my view, in addition to being a methodologically demanding and time-consuming procedure, this problem may be one of the most important reasons that functional mapping has low clinical relevance for motor therapy planning after cerebral lesions.

However, this problem might be overcome if we combine transcranial magnetic stimulation (TMS) with fMRI. In contrast to fMRI, TMS has an important impact on clinical diagnosis and development of a strategic plan for therapeutic intervention. To diagnose possible motor outcomes after cerebral lesions, besides the motor threshold or the mere feasibility of inducing relevant MEP amplitudes in the paretic limb, measurements of cortical facilitation have been increasingly relevant. Two examples are the steepness of the recruitment curve over a given representation site (Stinear et al., 2007; Ward, 2006) and interhemispheric interactions as measured with two temporally coupled stimulators (Butefisch et al., 2008). Both procedures are fast and highly clinically relevant, but have not become routine when planning motor therapy protocols. However, the direct stimulation of cortical areas without investigating its impact on the impairment of certain performances has limits. For example, transcranial stimulation of the intact hemisphere in patients who

*Corresponding author: Martin Lotze, M.D., Functional Imaging Unit;Center for Diagnostic Radiology and Neuroradiology, University of Greifswald; Friedrich-Löffler-Straße 23a, D-17487, Greifswald, Germany. Tel.: +49 3834 866899; Fax: +49 3834 866898; E-mail: martin.lotze@uni-greifswald.de.

experienced a capsular stroke in adulthood with high ipsilateral coactivation in fMRI does not evoke motor potentials from the ipsilateral, impaired hand (Foltys et al., 2003). In contrast, functional lesions of the ipsilateral side in these patients during complex motor performance demonstrate a relevant contribution of the intact hemisphere (Lotze et al., 2006).

The behavioural relevance of regional activation can be tested by temporary inactivation of target areas, for example with TMS, and subsequent analysis of the induced behavioural deficits (for the visual domain, see Cohen et al., 1997; for the motor domain, see Gerloff et al., 1998). This approach of interfering with behavioural function has also been referred to as "jamming." In contrast to invasive cortical stimulation with a spatial resolution of micrometers, the spatial resolution of TMS jamming is speculated to cover a field of centimeters (1–3 cm with a figure-eight coil with 120% of resting motor threshold (rMT) stimulus intensity with 0.5 Hz frequency; Desmurget et al., 1999), and the range of the pulse effect is limited to the cortical surface (approximately 1–5 cm). However, these values change drastically in accordance with the stimulation intensity. TMS induces a large, rapidly changing magnetic field and thereby delivers electrical currents in the brain in a plane parallel to the coil (Cohen et al., 1990), depolarizing the exposed neurons. TMS may also induce disruptive effects on ongoing regional cortical activity (Ziemann et al., 1996). This effect is not only due to adding general noise but actually induces a virtual lesion of underlying neuronal processes (Silvanto et al., 2007).

2. Main methodological considerations

2.1. Which area to stimulate?

For the motor system, several areas are easily accessible with a TMS coil without inducing intolerable direct stimulation of face and neck muscles. The most frequently investigated areas are the primary motor and somatosensory cortices, the dorsal premotor cortex (dPMC), the pre- and post-supplementary motor area (SMA) and the anterior and posterior parietal lobe (Schluter et al., 1998). Stimulation of the ventral premotor cortex (vPMC) and prefrontal areas is more problematic because stimulation induces painful direct muscle movement. Whether the cerebellum can be stimulated over the posterior fossa is still unclear (Ugawa, 2009).

2.2. How to navigate stimulation?

Only the primary contralateral motor cortex is precisely detected with a TMS pulse. For other areas, other methods are required for navigation. Navigation of the TMS coil over structural or functional maps improves spatial accuracy and allows stimulation of predefined areas outside of the primary motor cortex. The issue of the best method for navigating TMS pulses has been highlighted recently (Sparing et al., 2010). The authors suggest using a coregistered dataset of a high resolution anatomical and less spatially precise functional activation map to allow optimal spatial resolution for TMS navigation. Our lab uses the method of navigating on an individual overlay of an anatomical and functional map, with the latter gathered in a comparable task in the fMRI scanner, which will also be tested in the TMS laboratory (see Fig. 1).

However, other methods are also possible, such as orienting only on the cortical anatomical markers of the subject, although these markers may not be suitable for an altered representation map. In patients with cerebral lesions, methods such as this may not be optimal for tertiary regions that show high interindividual differences with respect to representation maxima for certain tasks.

Several tools for individual structural and functional navigation are commercially available. The methodological starting point for TMS functional investigation is a non-normalized, individual, anatomically coregistered activation map of the same cooperative, awake individual who will be investigated in the TMS laboratory. By using a localisation method for detecting anatomical markers affixed on the individual's surface and on the coil, a frameless navigation with the coil with spatial assignment to the dataset is possible.

2.3. What is the dependent variable?

Three different specificities for TMS-induced lesion effects may be isolated (Schlaak et al., 2007): (a) the task-specific lesion effect demonstrates an effect for a certain task but not for others (for example from the visual domain, form discrimination is unaffected but colour recognition is affected); (b) the time-specific lesion demonstrates a specific effect for a given temporal window (e.g., SMA jamming given 1 s before movement onset delays movement performance, but not if presented only 50 ms before movement onset.); and (c) the spatially-specific lesion demonstrates that only a certain region is functionally relevant, but others are not
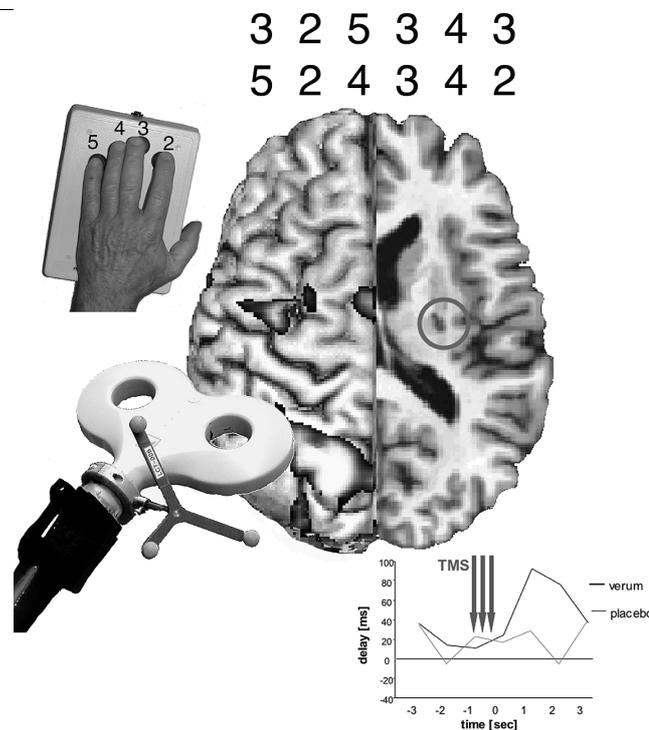
Fig. 1. Illustration of an overview on stimulation pattern, navigation data and behavioural response for an experimental setting investigating contralesional contribution of motor areas for the execution of finger sequences of the recovered hand after internal capsular stroke. The patient was asked to perform a sequence of finger movements indicated by numbers on a keyboard with a frequency of 1 Hz. fMRI during finger sequence performance was used for navigating on the individual functional map overlaid on the individual T1-weighted structural image. The coil and the subject are equipped with infrared 3D-reflectors, enabling a frameless navigation of the TMS-coil in the reference space of the patient. The right hemispheric axial slice shows the capsular lesion of this patient indicated with a circle. On the bottom an example of one single jamming event during the verum condition (here superior parietal lobe) and a placebo condition (for instance Sham stimulation with the coil 90 degrees flipped) is demonstrated. The verum stimulation resulted in a delay of the following finger tap with about 100 ms whereas the placebo stimulation showed no delay. A triple pulse of stimuli with an interstimulus time of 50 ms was used in this study (Lotze et al., 2006).

(e.g., the posterior parietal lobe for visuo-motor correction of target movements; Desmurget et al., 1999). Most frequently, a region-specific effect is tested. Here, two effects are predominantly observed if a virtual lesion was effective: a time delay, for example for the motor reaction paradigm (Day et al., 1989) or a change in performance (Lotze et al., 2006 for superior parietal jamming). The latter may be a decrease in performance, which is much more frequently observed when a functionally relevant area is jammed. With regard to stimulation over the primary visual cortex, this will induce perceptual losses, but with regard to stimulation over areas associated with precise motor coordination, stimulation may alter the processing of the target stimuli for the movement and also the sensorimotor transfer into a coordinated movement. Jamming the posterior parietal lobe during visual target movements with online movement direction changes may result in imprecise movement performance such as spatial inaccuracy

(Desmurget et al., 1999). However, even improvements in performance may be observed, for example during left but also right theta-burst stimulation of the dorsolateral prefrontal cortex (DLPFC) when an implicit performance task is followed by a secondary cognitive task. The interference with the latter can be diminished by jamming, resulting in increased performance of the implicit task (Galea et al., 2009).

2.4. Which TMS pulses will be used and when will they be applied?

2.4.1. Pulse number and frequency

Overall, three different methods for applying a lesion with TMS are known. The first is applying a single pulse above the resting motor threshold during task performance. Of course, this method is perfectly suited for detecting the precise time unit for functional interference of an area during a performance. The area below

the TMS coil depolarizes, and after a short period of high frequency discharge, neuronal activity is reduced for a period of 50–150 ms, which has been proposed to be the physiologic effect underlying a transient virtual lesion (Walsh and Rushworth, 1999). A good example of the temporal specificity of this effect is a virtual lesion above the visual cortex that suppresses a visual flash stimulus given 80–140 ms earlier (Cracco et al., 1990). These 80 ms are about the time a visual input needs to be processed in the primary visual cortex. For the motor system, a single TMS pulse applied to the motor cortex between the "go" signal and the motor response can delay the response for 50–100 ms (Day et al., 1989). In combination with a visual "go" signal, this optimal time window is about 140 ms for the anterior premotor, 180 ms for the posterior premotor, and 220 ms for the primary motor cortex (Schluter et al., 1998). However, the time delay also depends on the stimulus intensity, underlying the stimulus intensity dependence of depolarisation of stimulated neurons (Rothwell, 2003).

Trains of stimuli are more effective than a single pulse for inducing a functional lesion. This may be why partially contradicting results were obtained with a single pulse method (Johansen-Berg et al., 2002b; Werhahn et al., 2003) and protocols using multiple TMS pulses (Lotze et al., 2006). In addition, TMS trains induce longer virtual lesions resulting in a loss of temporal precision (Gerloff et al., 1998). In particular, if repetitive TMS (rTMS) is used for several seconds with high intensity, spatial precision is significantly reduced. The effect that excitability may be spread to other areas is a serious issue (Siebner et al., 2009). Therefore, Ziemann has suggested that TMS-induced alteration in performance proves the involvement of the stimulated brain region and the connected neuronal network in the investigated task (Ziemann, 2010).

Another interesting technique is the application after motor performance to induce a modulative effect on motor learning. For example, a 1 Hz rTMS pulse over M1 can abolish the effect of practice (Muellbacher et al., 2002) and therefore specifically disrupts the retention of the behavioural improvement. More recently, the indication of 1 Hz rTMS before task performance as a "functional lesion" effect has been questioned. Low-frequency rTMS does not necessarily decrease cortical excitability, for example when coupled with cathodal transcranial direct current stimulation (tDCS) applied in advance of rTMS (Siebner et al., 2004). Other strategies have been developed that result in stronger effects with shorter stimulation time. The theta-burst

technique offers these possibilities, and most authors consider that it potentially induces a functional lesion. Thus, this technique has the additional advantage that it can be applied before the motor task starts (Mochizuki et al., 2005).

2.4.2. Pulse intensity

The intensity of TMS pulses used should be selected so that the number and frequency of pulses applied differ with respect to the task tested. However, they are usually kept constant within cortical stimulation sites of each individual. Because cortical stimulation differs remarkably between individuals, it should be normalized to the individual motor threshold. The most frequently used intensities are 100 to 120% of the resting motor threshold for continuous repetitive stimuli (e.g., Desmurget et al., 1999; Lotze et al., 2006; Lotze et al., 2009). For theta-burst rTMS 80% of the active motor threshold was demonstrated to be highly effective (Mochizuki et al., 2005) which suggests that this stimulation frequency is much more effective than others. Further systematic comparisons are necessary for the behavioural effects of jamming using single, double, and triple pulses. However, for the 1 Hz rTMS stimulation, comparisons of TMS intensity and coil selection reported a significant effect for the suprathreshold intensity of 115% of rMT but not for the subthreshold intensity of 90% of rMT for two different figure-eight coils over the dPMC (Lang et al., 2006).

One must be aware that stimulation of more than 100% of rMT near the primary motor cortex may induce movement artefacts that have to be controlled using a control paradigm (for example, by direct muscular stimulation inducing the same movement effect).

2.5. Control conditions

Transient "jamming" of cortical activity by TMS has the advantage of allowing for drawing conclusions about the functional relevance of regional neuronal activation for a given behavioural task (see Cohen et al., 1997). However, the focal specificity of this method critically depends on the use of adequate control conditions. The impact of noise is controlled in most investigations by stimulation with the coil over CZ flipped 90 degrees, usually called "sham stimulation." However, when participants are asked how aversive these stimulations are, they rate them very low. Anterior prefrontal stimulation may control for cutaneous sensations. It is important to locate these control areas cautiously because a more anterior location elicits increased muscle

artefacts but a more posterior location may stimulate the pre-SMA. Other areas such as the inferior lateral frontal lobe (or the inferior parietal lobe) may be suitable too, dependent on the task used. Peripheral stimulation may control for possible distraction due to movement effects of the non-performing hand, especially with stimulation above the resting motor threshold and near M1. For the decision of "pathologic functional overtake," comparison of the response of a patient group with an age-matched group of healthy controls is essential. For example, when testing reorganisation in patients after cerebral lesions, the same experimental setting should also be performed in age-matched controls.

Stimulation of different regions requires different placebo or sham conditions. If the parietal lobe is stimulated, a sham condition with a 90-degree flipped coil over CZ may be acceptable. When stimulating with suprathreshold intensity over M1, induction of movement must be considered, and when stimulation is carried out above areas with direct effects on the face or neck muscles, the control regions should control for that. It may be useful to use visual analogue scores for controlling for aversive feeling during jamming and feeling of an impact on the performance tested. These scores should be balanced between verum and placebo conditions. Figure 2 provides an example of the rating of 14 participants about an aversive and disruptive effect after triple pulse stimulation with 120% of rMT over several different cortical areas.

However, when comparing different functional effects between two areas, the involvement of placebo jamming areas is not absolutely necessary. Davare and colleagues (Davare et al., 2006) tested the function of the vPMC (BA 44; pars opercularis) versus the dPMC (anterior part of the anterior gyrus at the border of the sulcus frontalis superior) for precision grasping. They used paired pulse TMS with 120% rMT over the vPMC or dPMC anatomically, and navigated and found a dissociation of functional relevance in precision grasping. Bilateral vPMC jamming resulted in modifications in grip size, but left dPMC lesions modified the timing of the lifting phase. This study provides a good example of how jamming by anatomical navigation without orientation to individual functional maps is capable of differentiating complex motor functions in humans.

3. Using virtual lesions in patients with cerebral lesions

Studies addressing the functional relevance of areas with increased fMRI-based activity in stroke pa-

tients are scarce. Single-pulse TMS over the primary motor cortex (M1) of the affected hemisphere results in increased reaction times, especially in patients who showed good motor recovery (Werhahn et al., 2003). The same technique used over the dPMC of the affected hemisphere demonstrated a contribution of the dPMC to recovered simple motor behaviour (Fridman et al., 2004). With respect to the non-affected hemisphere, single-pulse TMS application during a simple reaction time task indicated a role for the dPMC (Johansen-Berg et al., 2002b) in motor recovery. In particular, this phenomenon was observed in patients who suffered from a higher degree of motor disability (Johansen-Berg et al., 2002a). In an investigation of patients who had almost recovered from motor impairment after capsular stroke, we applied TMS jamming to several motor regions of the non-affected hemisphere as well as the affected hemisphere. Seven patients executed a previously learned finger movement sequence with the recovered hand (Lotze et al., 2006). We used this complex motor paradigm because an increased contribution of motor areas within the hemisphere ipsilateral to movement execution was expected during highly complex finger movements (Foltys et al., 2003). In addition, a later study demonstrated that differences in activation patterns between patients and controls are more pronounced when more complex tasks are employed (Schaechter and Perdue, 2008). TMS was stereotactically navigated on the basis of 3D-reconstructed individual MRI data and individual fMRI-activation maps assessed during the same motor task. The effects of TMS bursts on complex finger sequences were compared in patients and age-matched healthy controls for timing errors and accuracy of performance. Stimulation over the dPMC, the primary motor cortex (M1), and the superior parietal lobe (SPL) of the affected and the non-affected hemispheres resulted in significant interference with recovered performance (affected hand) in patients. Although interference with the dPMC and M1 induced timing errors only, SPL stimulation caused both timing and accuracy deficits. In healthy controls, no jamming effects over the hemisphere ipsilateral to movement performance were observed. Therefore, this study points to a persistent beneficial role of the dPMC, M1, and SPL of the contralesional hemisphere for the cortical control of effectively recovered complex motor behaviour in stroke patients.

In another study (Lotze et al., 2009), we examined whether increased ipsilateral activation in motor areas contributes to movement performance of complex movements in a group of patients suffering form
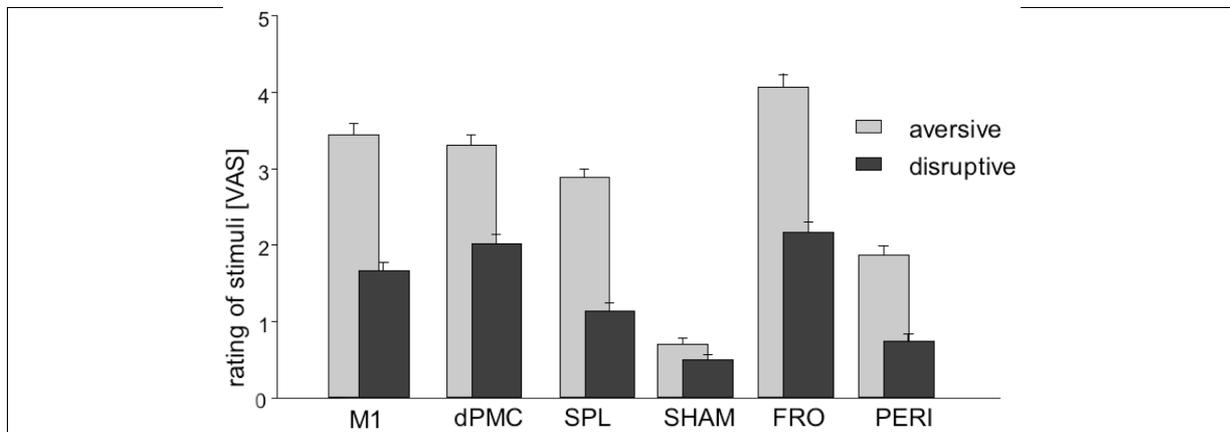
Fig. 2. Rating of aversiveness (light grey) and disruptiveness (dark grey) of 120% rMT triple pulse stimuli over the primary motor cortex (M1), the dorsal premotor cortex (dPMC), the superior parietal lobe (SPL), the coil over CZ flipped 90 degrees (Sham), prefrontal stimulation (FRO), and peripheral stimulation of the finger extensors in the height of the forearm (PERI) with an intensity inducing comparable muscle effects similar to M1 stimulation. Importantly, the control for auditory only output of the coil induced less aversive effects in the participants, and is therefore often not a relevant placebo condition. Within the control stimuli, the prefrontal cortex (FRO) was highly aversive and disruptive.

congenital hemiparesis due to unilateral defects in the periventricular white matter. Therefore, we investigated four of these patients with highly homologous lesion location, lesion size, and maturational stage of the brain at the time of the insult. In addition, patients did not show any motor potentials in the affected hand evocable from single pulse TMS over the primary motor cortex of the contralesional hemisphere. We used the same method as in the previous experiment (Lotze et al., 2006) to investigate whether increased ipsilateral activation during finger movements of the paretic hand contributed to movement performance. Functional lesions of the dPMC and M1 but not SPL of the contralesional hemisphere induced decreased temporal precision of finger sequences. Our results argue for a possible role for the dPMC and M1 of the contralesional hemisphere in complex motor behaviour even in patients with congenital hemiparesis who control their paretic hands via crossed cortico-spinal projections from the damaged hemisphere.

Stoeckel and Binkofski (Stoeckel and Binkofski, 2010) recently discussed the controversial findings between the report of lower outcome of chronic stroke patients with increased activation of the non-affected hemisphere and the functional role of activation sites in the non-affected hemisphere for complex finger movements in well-recovered patients. They suggested that some of the incongruent findings may be dependent on the complexity of the motor task used for experimental testing. In addition, they stated that some areas may be temporarily relevant to movement execution until the partially lesioned structures regain their func-

tion. Therefore, it is extremely useful to test patients over time and not only in the chronic state. However, fMRI-experiments alone may not sufficiently provide answers to that question. We are currently not even sure how best to control task difficulty, either by trying to keep the task identical across all participants (Schaechter and Perdue, 2008) or the effort to accomplish the task (Ward et al., 2003). Therefore, work with TMS jamming of movements with different complexity in patients who experienced motor impairment after a well-defined cerebral lesion is highly important. We are currently testing the functional role of motor areas in the affected and non-affected hemisphere in chronic subcortical stroke patients and also in healthy controls for different complex movements to detect more detailed patterns of possible overtake of motor function after cerebral damage (Lotze et al., 2010).

4. Concluding remarks

Although applying functional lesions has methodological limitations and is not easy to perform, especially in a clinical setting, this technique offers the strong possibility of understanding the mechanisms of recovered motor function. In addition, this technique produces evidence of the functional relevance of individual areas, especially when coupled with fMRI navigation. After further methodological work on the effect of different jamming techniques, application of virtual lesions will have an increasing role in the investigation of recovered motor function.

Acknowledgements

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