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CHAPTER 21

Exploring paradoxical functional facilitation with TMS

Hugo Théoret, Masahito Kobayashi, Antoni Valero-Cabre and Alvaro Pascual-Leone*

Laboratory for Magnetic Brain Stimulation, Beth Israel Deaconess Medical Center, Harvard Medical School, 330 Brookline Avenue, Boston, MA 02215 (USA)

1. Introduction

Current theories about the representation of function in the brain are increasingly dominated by the notion of distributed neural networks, a series of assemblies of neurons that might be widely dispersed anatomically but are structurally interconnected and can be functionally integrated to serve a specific behavioral role (Mesulam, 1990, 2000). Certain distributed networks subserving specific functional domains can be identified. For example, spatial attention appears to be supported by the parietal lobes connected by callosal fibers and via the inferior colliculus, the prefrontal cortex (particularly on the right) and cingulate gyrus, along with connections via the superior occipito-frontal fasciculus and the cingulum. Another common example is language, subserved by Broca's and Wernicke's areas in the dominant hemisphere and connections along the arcuate fasciculus and the extreme capsule. However, it is important to recognize that depending on behavioral demands, neuronal assemblies can be integrated into *different* functional networks by shifts in weighting of connections (functional and effective connectivity). Indeed, *timing* of interactions between elements of a network, beyond integrity of structural connections, might be a critical binding principle for the functional establishment of given network action and behavioral output (Engel and Singer, 2001). Such notions of dedicated, but multifocal, networks, which can dynamically shift depending of demands for a given behavioral output, provide a current resolution to the long-standing dispute between localizionists and equipotential theorists. Function comes to be identified with a certain pattern of activation of specific, spatially-distributed but interconnected neuronal assemblies in a specific time window and temporal order. In such distributed networks, specific nodes may be critical for a given behavioral outcome. Knowledge of such instances is clinically useful to explain findings in patients and localize their lesions, but provides an oversimplified conceptualization of brain-behavior relations. We may be better served realizing that behavior is never the result of the lesion, but rather the consequence of how the rest of the brain is capable of sustaining

* *Correspondence to*: Dr. Alvaro Pascual-Leone, Department of Neurology, Beth Israel Deaconess Medical Center, 330 Brookline Avenue, KS-454, Boston, MA 02215, USA
Tel: 617-667-0203; Fax: 617-975-5322
E-mail: apleone@bidmc.harvard.edu

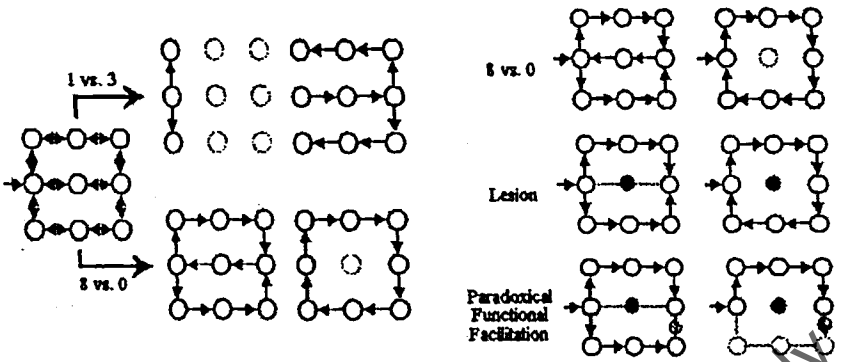

Fig. 1. Schematic representation of the hypothesized effects of a lesion in a distributed network. After the first lesion state, 0 and 8 are no longer distinguishable because they share the same activational pattern caused by the the modified spread of activation due to the lesion, whereas the second leasion re-establishes different activation patterns, and only the difference, not the exact pattern itself, is important for the distinction of the states.

function following a given lesion. This provides a conceptual framework to explain instances of paradoxical functional facilitation (Kapur, 1996), when a second lesion can restore behavioral integrity (e.g. Villeumier et al., 1996).

Imagine, for example, a distributed neural network made up of nine assemblies of neurons (nodes) and their connections (Fig. 1). A given behavior might be to differentiate between a state '1' and a state '3'. A different behavior, supported by some of the same neuronal assemblies but engaged into a different network might be to differentiate '0' from '8'. In the later case, a lesion to one, and only one neuronal assembly will cause a failure of the behavior and we might be tempted to conclude that '8' is localized in that one node, a conclusion that would certainly be incorrect despite the reality of the behavioral impact of the focal, single 'lesion'. In this dysfunctional state, a second 'lesion' may restore the ability to differentiate '0' from '8', hence paradoxically restoring function, even though the new expression of '0' and '8' may well be different.

In this chapter, we wish to first briefly describe experiments conducted in cats to underscore the local and distant effects exerted by repetitive TMS. The better understanding of the modulatory effects of rTMS can then lead to the experimental testing of specific hypotheses relating to the paradoxical effects of TMS-induced 'virtual lesions'. We will then describe studies on attention and motor performance that highlight the potential of TMS as a tool to reveal functional facilitations and ultimately offer the possibility to use such an approach for therapeutic purposes. Kapur had predicted this potential of TMS for the systematic exploration and therapeutic utilization of paradoxical facilitations in the human brain (Kapur, 1996; Ovsiew, 1997). We believe that we are now at a stage where such work ought to be conducted.

2. Repetitive stimulation and the creation of 'virtual lesions': animal evidence

Transcranial magnetic stimulation (TMS) provides a means of interfering with the activity in a specific cortical area and probing the functional changes that may result. The effects can be transient or extend beyond the duration of a train of stimuli, depending on the parameters of stimulation. Applied as trains of repetitive stimuli at appropriate frequency and intensity, TMS can be used to transiently disrupt the function of a given cortical target thus creating a temporary, "virtual brain lesion" (Pascual-Leone et al., 1999). The use of repetitive TMS (rTMS) to

disrupt brain function stems from studies of the motor cortex, where it has been shown that applied to the primary motor area, a train of TMS pulses at a frequency of 1 Hz induces a transient reduction of cortical excitability in most subjects that outlasts the stimulation itself (Chen et al., 1997; Maeda et al., 2000). The notion that cortical excitability can be reduced in the motor cortex following low-frequency rTMS suggested that it could also modulate behavioral output when applied to non-motor areas. This idea was first applied to the visual cortex, where it was shown that a 1 Hz, 10 min rTMS train to the occipital pole could impair performance in a visual perception and imagery task (Kosslyn et al., 1999). This rationale has since then been applied to a variety of cortical areas, including parietal (Hilgetag et al., 2001; Lewald et al., 2002; Sack et al., 2002; Brighina et al., 2003), somatosensory (Satow et al., 2003), visual (Thut et al., 2003) and prefrontal (Mottaghy et al., 2001; Robertson et al., 2001; Shapiro et al., 2002) cortices, as well as to the cerebellum (Théoret et al., 2001).

This approach, which is devoid of the usual caveats associated with lesion studies (size of lesion, general cognitive impairments, plastic brain reorganization, etc.) (Robertson et al., in press) should also allow the investigation of paradoxical functional facilitations. However, regardless of the frequent and extensive use of rTMS for the study of cognitive functions in the human cortex, not much is yet known about its effects on networks of neural cells active during the development of a cognitive task. Animal studies should be used to answer questions that cannot be easily addressed in human subjects because of methodological or safety limitations.

Confirming that certain regions of the animal brain, such as the motor cortex, respond in a similar way as the human when targeted with (r)TMS is a critical first step to validate the model. The development of such an animal model is not a straightforward project. Four important aspects need to be taken into account to be able to generate information that can be extrapolated from animals to humans. First, the ratio of the size of the TMS coil over the size of the head and brain of the animal needs to allow specific stimulation of areas with differential contributions to a task. This question poses technical limitations since smaller coils have less penetration power and may thus activate the brain differently. Second, the animal species chosen should be able to be kept and manipulated in relatively large numbers in order to control for the impact of interindividual variability of the TMS effects. Animals have to tolerate single and repetitive TMS at low- and high-frequencies in an awake state or, if anesthesia is needed, at anesthesia levels that do not significantly interfere with the cortical function of the area of interest. Training to get the animal accustomed to the TMS at different intensities and frequencies is needed to avoid confounding aspects such as stress, particularly when dealing with cognitive functions. Third, it has to be possible to record the effect of TMS by means of neurohistological, electrophysiological (motor evoked potentials, evoked neuronal field potentials) and imaging techniques (2 deoxiglucose uptake, optical imaging intrinsic signal). Ideally, it should be possible to induce similar behavioral disruptions as those shown in equivalent tasks in humans so as to be able to establish a detailed correlate between behavioral and neurobiological effects. Finally, an extensive knowledge of the anatomy and function of cortical and subcortical networks involved in a task in that particular animal species is fundamental in order to interpret the impact of TMS. Obviously, previous anatomical, functional and behavioral data of the metabolic and behavioral impact of the same areas by irreversible (lesions) or reversible (pharmacological studies, cooling probes) deactivation techniques will help enormously in the interpretation of TMS results.

We have developed an animal model that meets these criteria and allows the study of TMS-induced behavioral, metabolic, and electrophysiological disruption in an awake preparation (Valero-Cabre et al., 2002). Motor evoked potentials (MEPs) can be easily and consistently recorded after TMS of the primary motor cortex (Fig. 2a). The MEPs have amplitudes and latencies consistent with those observed in humans (Figs. 2c, 2d). Moreover, low frequency rTMS but not sham stimulation of the

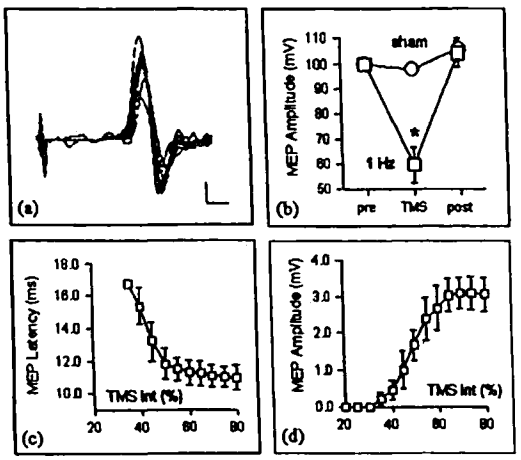

Fig. 2. (a) Overlapped motor evoked potentials recorded in the right flexor radialis muscle of the awake cat by consecutive TMS pulses delivered in the left primary motor cortex. Horizontal bar: 3 ms, vertical bar: 1 mV. (b) Average modulation of the MEP amplitude in three awake cats prior (pre), immediately after (TMS) and 20 min after (post) two conditions: 1 Hz stimulation during 15 min (900 pulses) or sham stimulation at identical parameters, both over the left primary motor cortex; * $p < 0.05$ vs. pre- and post-MEP amplitudes. (c) Changes in onset latency of the MEP at increasing levels of intensity of stimulation (% vs. maximal TMS machine output). (d) Recruitment of MEP amplitudes at increasing levels of TMS intensity.

primary motor cortex is able to inhibit contralateral MEP responses (Fig. 2b), much as is the case in humans (Chen et al., 1997; Maeda et al., 2000). Neuroimaging data in humans, using PET or fMRI, are limited by methodological constraints and artifacts that affect the detailed spatial and temporal resolution of the TMS impact. Overcoming these limitations, the feline model has been used successfully to examine the metabolic impact of on-line rTMS. Valero-Cabre et al. (2002, 2003) stimulated two cats with real 20 Hz rTMS and one cat with sham rTMS for 28 min in the visuo-parietal (VP) cortex area implicated in visual attention. We found a decrease in the uptake of ^{14}C-radiolabeled glucose in the targeted cortical area (Fig. 3a) compared to analogous structures in the contralateral hemisphere. Moreover, a transsynaptic deactivation of several targets receiving strong afferent connections and located far away from the reach of the direct effect of the magnetic field was found in the superior colliculus (SC) (Fig. 3b) and the splenial visual area (SVA) (Fig. 3c). It is worth mentioning that the direct impact on cortical areas was significantly greater the transsynaptic impact and that the transsynaptic effect was highly specific along known anatomical connections, proportional in its magnitude with the strength of those connections, and in all cases led to a suppression of activity in the distant structures. Control structures with less or no connections to the directly stimulated area VP, such as the inferior colliculus (IC), medial geniculate (MGN) and lateral geniculate (LGN) nuclei showed no change in the 2DG uptake (Fig. 3d). These results, match cooling deactivation experiments of the same areas in the cat (Vanduffel et al., 1997) and demonstrate a remarkably precise spatial resolution of TMS. Furthemore, in agreement with the function attributed to the VP area in cooling deactivation experiments, slow frequency stimulation (1 Hz) for 15 min in the awake cat induces a reversible neglect in the contralateral visual field, in agreement with studies in normal humans (Hilgetag et al., 2001) (Fig. 3e).

3. Dirsupting the brain with TMS to improve behavior

3.1. Attention

Brain plasticity following a brain lesion may not lead to recovery but rather provide the substrate for deficits to become chronically established. In such instances, focal disruption of brain activity may lead to behavioral improvement. For example, some patients with unilateral right brain damage suffer from extinction, a condition in which stimuli delivered to the contralesional side are not perceived when a simultaneous ipsilesional stimulus is presented (Vallar, 1998). It has been hypothesized that this phenomenon of "extinction to double simultaneous stimulation" and "neglect" is related to an imbalance between the hemispheres resulting from the release

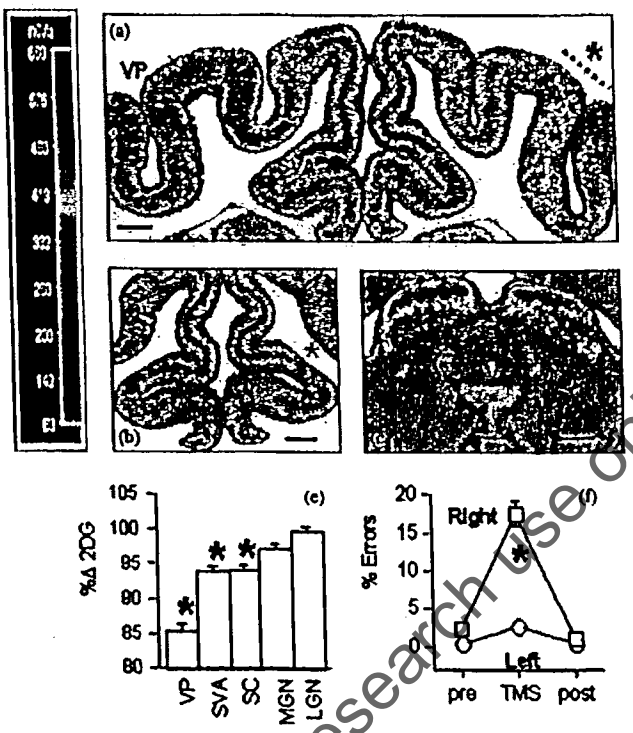

Fig. 3. (a) ^{14}C-2 deoxiglucose (^{14}C-2DG) autoradiography from a cat brain submitted to 20 Hz rTMS of the left visuo-parietal cortex (*). Note differences between the stimulated (left *) and the non-stimulated (right) hemisphere. (b) Detail of the transynaptical impact of rTMS on the left splenial visual area (SVA) (*). (c) Detail of the rTMS effect on the left superior colliculus (SC) (*). (d) Average percentage of change with respect to the analogous area in the contralateral hemisphere of the ^{14}C-2 deoxiglucose levels in visuo-parietal cortex (VP), splenial visual area (SVA), superior colliculus (SC), medial geniculate (MGN) and lateral geniculate (LGN) nuclei. * $p < 0.01$ vs. contralateral hemisphere. (d) Number of errors in the detection of visual stimuli presented in the right and left visual hemifields before (pre), during the 15 min following 1 Hz rTMS stimulation at 40% on the VP cortex (TMS) and 60 min after the end of the stimulation. Note the increase in the number of mistakes in detecting visual stimuli in the right but not the left visual hemivfield. L = left, R = Right hemisphere. (*) stimulated hemisphere. Scales bars = 2 mm.

of reciprocal inhibitory influences (Kinsbourne, 1977). Lesion of one hemisphere results in trans-hemispheric release of inhibition onto the healthy hemisphere that becomes "hyperactive", creating "hyper-attention" to the ipsilesional side. In humans, support for this hypothesis first came from the report of a patient who suffered from severe spatial neglect (the failure to explore contralesional space) following a right parietal lesion (Vuilleumier et al., 1996). Following a second lesion to the left frontal cortex, the neglect symptoms completely and abruptly disappeared, lending creedence to the notion of a dynamic balance between the two hemispheres for the allocation of attentional resources. Animal studies by Sprague and later Payne and Lomber (Sprague, 1966; Payne et al., 1996) have provided critical insights into the underlying physiology.

Oliveri et al. (1999) took advantage of the non-invasive nature of single pulse TMS to re-visit the famous case described by Vuilleumier et al. (1996).

If failure to orient to the contralesional side is the result of hyperactivity of the healthy hemisphere, then transient disruption of left cortical areas in right parietal-damaged patients may also temporarily alleviate extinction symptoms. In a group of 14 right brain-damaged patients, it was shown that application of single-pulse TMS to the left prefrontal cortex significantly reduced contralateral extinction when the TMS pulse was applied 40 ms after bilateral electrical stimulation of the fingers. These results were later replicated by the same group in a visuospatial task using high-frequency repetitive TMS (Oliveri et al., 2001). The performance of five right brain-damaged patients in a line bisection task was significantly improved following parietal rTMS of the unaffected hemisphere. Again in right brain-damaged patients suffering from visuospatial neglect, Brighina et al. (2003) set out to determine if a two-week regimen of low-frequency repetitive TMS to the healthy hemisphere could reduce visuospatial neglect beyond the period of stimulation. This protocol was based on experimental data showing significant reduction of depressive symptoms following a two-week low-frequency rTMS treatment of the left prefrontal cortex in medication resistant depressed individuals (see Wassermann and Lisanby, 2001). One hertz rTMS was applied to the left parietal cortex in three patients with a right parieto-temporal lesion every other day for 14 days. Visuospatial performance (clock drawing and line bisection tasks) was significantly improved immediately after treatment and for at least 15 days. The authors interpreted these results as additional evidence for the idea that hyper-excitability of the unlesioned hemisphere may underlie neglect syndromes and that inhibition of these overactive areas, whether transiently with single-pulse TMS, for a few days with repetitive TMS or permanently with a second lesion, may restore function.

The concept of reciprocal inter-hemispheric inhibition and its link to attentional performance was further investigated with rTMS in normal subjects (Hilgetag et al., 2001). Here, it was hypothesized that visual spatial attention could be improved following transient cortical impairment in healthy subjects. Indeed, one might speculate that the disinhibition of structures involved in inter-hemispheric competition might lead to a functional release in the opposite hemisphere, which could result in a measurable behavioral enhancement. To verify this hypothesis, normal subjects had to detect small rectangular stimuli briefly presented on a computer monitor either unilaterally in the left or right periphery, or bilaterally in both. Spatial detection performance was tested before and immediately after a ten minute, 1 Hz rTMS train to: (a) right parietal cortex; (b) left parietal cortex; (c) right primary motor cortex; and (d) sham stimulation. We observed a clear extinction phenomenon for stimuli presented contralaterally to the stimulated hemisphere (right or left parietal cortex). This deficit was accompanied by increased detection for unilateral stimuli presented on the side of the stimulated hemisphere compared to baseline (Fig. 4). None of the control stimulation sites had any effect on the detection performance. Detailed investigation revealed that although trends were mirror-symetric for rTMS of left and right parietal cortex, the enhancement produced by right-hemispheric rTMS was significantly greater than that after left hemisphere and only right hemispheric stimulation produced a significant ipsilateral detection enhancement. These data suggest that in normal subjects, decreasing left parietal cortex excitability with rTMS disinhibits the contralateral cortex leading to improvements in performance.

3.2. *Motor performance*

The paradoxical effects of rTMS-induced 'virtual lesions' are not limited to studies of attention. For example, we have recently showed a motor cortex effect similar to that observed in parietal areas. Patients with strokes involving the primary motor cortex (M1) often display increased excitability of the contralateral M1 and intracortical inhibition is generally suppressed, presumably through impaired transcallosal inhibition (Traversa et al., 1997; Shimuzu et al., 2002). Single-pulse TMS studies have revealed mainly inhibitory interactions between both primary motor cortices (Ferbert et al., 1992; Gerloff

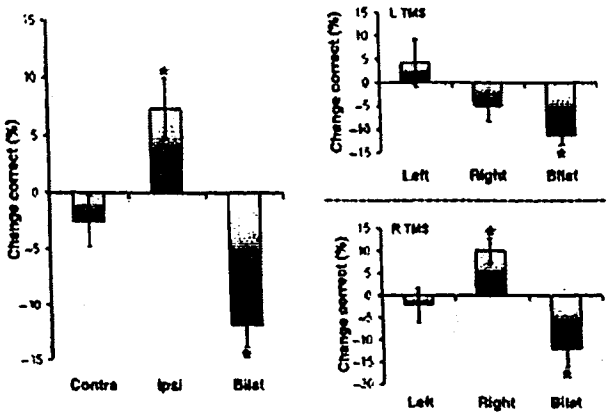

Fig. 4. Modified from Hilgetag et al. (2001) with permission. Changes in correct stimulus detection after parietal rTMS. The diagrams are based on changes in the number of correctly detected stimuli (relative to the total number of presented stimuli) averaged for both stimulus sizes and all subjects. (a) The pooled data show a significant increase in performance ipsilateral to the parietal rTMS location (increase in relative percentage points: 7.3% SEM: 2.6%), and a trend to decreased contralateral performance (reduction by 2.5%, SEM: 2.3%). In addition, detection of bilateral stimuli decreased significantly (–11.7%, SEM: 2.0%). These trends are also apparent after separating data for (b) left parietal TMS and (c) right parietal rTMS. Significant trends (as determined by z-tests, are marked by stars.

et al., 1998) and we thus hypothesized that low-frequency rTMS over M1 might lead to the disinhibition of the contralateral M1, and the subsequent improvement in motor performance. Indeed, it was shown that following 10 mins of 1 Hz rTMS, execution times in a well-learned key-pressing task were significantly shortened for the hand ipsilateral to the magnetic stimulation compared to baseline performance (Fig. 5a). Performance in the contralateral hand remained unchanged and we observed increased intracortical excitability in the un-stimulated M1 (Fig. 5b). It does appear that a phenomenon of interhemispheric rivalry, as postulated for attentional processes, is also at play between motor cortices, whereby suppression of the excitability of one motor cortex can enhance motor performance with the ipsilateral hand through, presumably, suppression of transcallosal inhibition.

4. Conclusion

Taken together, these results underscore the potential of TMS as a tool to probe the paradoxical functional facilitations that may occur following lesions to a particular node of a complex and distributed neural network. Work in cats has shown the robust metabolic effects of rTMS on local and distant cortical and subcortical sites. This has important implications for the study of paradoxical functional facilitations in human subjects since improvements in performance following a cortical lesion are often believed to result from plastic changes occuring in parts of a distributed network functionally related to the lesioned area (Kapur, 1996). TMS work on attention and motor performance in human subjects has highlighted the mechanisms that may underlie functional facilitations by providing experimental support for the hypothesis that some brain functions operate in a state of dynamic hemispheric competition. Manipulation of the hemispheric balance with single or repetitive TMS affords the investigation of the neural mechanisms underlying plasticity following brain lesions and can provide valuable knowledge on the inner workings of the normal brain. One can hope that these ideas will result in the development of meaningful therapeutic approaches, such as the

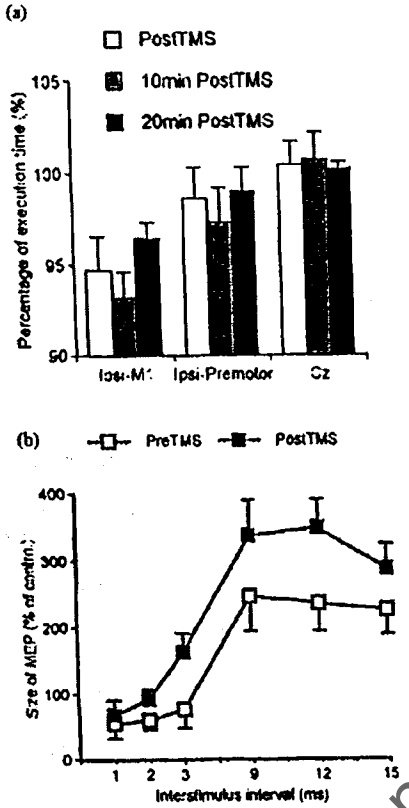

Fig. 5. (a) Ratio of execution times following rTMS at three different sites (ipsilateral M1, ipsilateral premotor cortex and Cz). Reaction times were significantly shorter after ipsilateral rTMS over primary motor cortex. (b) Changes in MEP sizes of the left first dorsal interosseus muscle with various interstimulus intervals.

treatment of motor, attentional and language impairments associated with strokes.

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