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Contribution of transcranial magnetic stimulation to the understanding of mechanisms of functional recovery after stroke

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Abstract

Motor disability continues to be a major cause of morbidity after stroke. The neural underpinnings of disability and of functional recovery are still unclear. Here, we review recent evidence obtained using transcranial magnetic stimulation (TMS) that provides new insight into these mechanisms. We briefly discuss the use of TMS in the diagnosis, prognosis, and therapy of post-stroke motor disability. Differently from previous reviews, particular emphasis is placed in the discussion of the use of TMS as a tool to explore in detailed mechanisms of neuroplasticity during spontaneous and treatment-induced recovery of motor function. TMS can be used to acquire the understanding of these mechanisms required for the development of more rational and clinically useful interventions in stroke neurorehabilitation.

Introduction

The problem

Stroke continues to be the leading cause of long term disability in the U.S. [1] Primarily due to a loss of motor abilities and subsequent impairment in activities of daily living, stroke is estimated to cost the U.S. over two trillion dollars in the next fifty years[2]. These economic and social costs are not restricted to the intensive acute care that occurs with stroke, but rather is outweighed by later outpatient costs and is highly correlated with the level of disability [3]. Taken together, these statistics emphasize the need for interventions designed to improve post-stroke neurorehabilitation [4]. While recent advances in stroke care have primarily been concentrated on the neuroprotective and neurovascular fronts [5,6], tools used to study and alter cortical function have played a significant role in all parts of post-stroke care: diagnostic, prognostic, and interventional. In this review, we will examine how transcranial magnetic stimulation (TMS) can be used to dissect the physiologic mechanisms underlying motor deficits, spontaneous motor recovery, and the beneficial effects of therapeutic interventions. An understanding of these neurobiological foundations will likely enhance our abilities to diagnose, prognosticate, and treat post-stroke motor disabilities.

TMS as a technical tool

Since the first reported use of TMS in humans[7], it has been clear that this tool would enhance understanding of the nervous system and find application in medical treatment of nervous system disorders. Working via the principles of electromagnetic induction, standard TMS instruments consist of a high voltage capacitor which can be discharged through an insulated

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coil of wires [8-10]. The rapid, time-varying magnetic field created around the coil, which passes unchanged through electrically-resistant structures such as the skull, can be used to induce an electrical current in human brain tissue. When a TMS coil is placed on the scalp over primary motor cortex (M1), the induced electrical current stimulates the neurons of the cortex [11]. When first applied to stroke patients, TMS was envisioned as a less painful alternative to transcranial electrical stimulation for the assessment of the impaired corticomotoneuronal pathways [12], however it soon became clear that fundamental differences in the physiological effects of TMS compared to electrical stimulation could allow more elaborate investigations [13,14].

Electrophysiological measurements available with TMS

TMS activates a mixed population of inhibitory and excitatory cortical interneurons which can affect local and remote pyramidal tract neurons. The frequency, intensity and coil orientation at which TMS pulses are delivered to the cortex significantly affect its consequences and its uses. Generally, when TMS pulses are delivered at frequencies less than 0.3Hz, it is for measurement purposes and has not been found to alter motor cortical excitability for prolonged periods of time as long as the motor system is at rest at the time of stimulus delivery [15,16]. However TMS stimuli applied to resting M1 at or above 0.3Hz [17] and paired pulses 1.5ms apart given in trains of at least 0.2Hz [18] have been found to alter cortical excitability beyond the period of stimulation. All of these and other forms of repetitive TMS (rTMS) can be used in an interventional manner to purposely alter cortical excitability both in a facilitatory and inhibitory way, in an attempt to change function of the underlying stimulated cortical tissues . The following represent some of the most common TMS measures used after stroke to dissect the physiologic mechanisms underlying motor deficits, spontaneous motor recovery, and the beneficial effects of therapeutic interventions.

Motor evoked potentials (MEP)—When TMS is applied at intensities above motor threshold, the activation of excitatory interneurons can result in volleys of upper motor neuron activity which subsequently activate alpha motor neurons of the spinal cord. The summed activity, an MEP, is measured via electromyography (EMG) from surface or needle electrodes over or in the muscles of interest [19], or as descending volleys of direct (D) or indirect (I) waves recorded directly from epidural electrodes over the spinal cord, close to the pyramidal tract [20,21]. The amplitude, area under the curve, and latency of MEPs are all used in various ways to measure motor cortical excitability.

Resting motor threshold (rMT) is defined as the intensity of stimulation required to produce an MEP of small amplitude in 5 out of 10 trials [19].

Stimulating M1 at different stimulus intensities (relative to rMT intensity or maximum stimulator output) creates an input/output or recruitment curve of MEP amplitudes [22,23] that is usually sigmoidal in shape. rMT is predominantly influenced by mechanisms of neuronal membrane excitability, evidenced by its alteration in the presence of pharmacological modifiers of sodium and calcium channels and relative stability in the presence of modifiers of synaptic transmission [24-26]. rMT also correlates with measures of white matter microstructure [27]. In contrast, recruitment curves are contributed to by changes in synaptic excitability, as evidenced by their alteration in the presence of pharmacological modifiers of synaptic transmission [23,28].

Short-interval intra-cortical inhibition (SICI) and facilitation (SICF)—Exploiting TMS' preferential activation of interneurons and transsynaptic activation of pyramidal tract cells has allowed for a better characterization of inhibitory and facilitatory mechanisms operating within M1. Paired pulse stimulation delivered through the same magnetic coil over

M1, where a suprathreshold test stimulus (TS) is preceded by a sub- or supra-threshold conditioning stimulus (CS), can be used to gain insight into the relative contribution of local inhibitory and excitatory inputs to M1 pyramidal tract cells. The CS can cause an increase in MEP amplitude (facilitation, SICF) or decrease in MEP amplitude (inhibition, SICI) compared to the MEP evoked by the TS alone. Inter-stimulus intervals of approximately 1.5-3ms cause attenuation of MEP amplitudes or SICI [29], which seems to be at least partially GABA-A receptor mediated [21,30-33]. With longer inter-stimulus intervals (~6-10ms) it is possible to observe a facilitation of MEP amplitudes, referred to as SICF [34], a more heterogeneous measurement that may have a significant spinal component [35]. One additional measurement that has been proposed as useful has been the determination of recruitment curves of SICI, a method perhaps underutilized that is likely to call for more attention in the future[36,37].

Another test of intracortical inhibition is the contralateral cortical silent period (CSP), a drop in background voluntary EMG activity which occurs when a suprathreshold TMS pulse is delivered to the M1 contralateral to a muscle that is voluntarily activated. It has been proposed that the later part of the contralateral CSP [38] is a GABA-B receptor mediated cortical phenomenon [24], and hence likely represents a separate inhibitory network or mechanism within M1 relative to SICI [30].

Inter-hemispheric inhibition (IHI)—The inhibitory interactions between the two M1s can be evaluated using a paired pulse technique [39], where a suprathreshold CS is applied over the conditioning M1 at about 10ms prior to the TS applied to the conditioned M1. While other inter-stimulus intervals have been used, the 10ms interval has been the most widely studied (IHI_{10}). IHI_{10} is likely mediated via transcallosal glutamatergic neurons from the conditioning M1 interacting with local GABA-B receptor mediated inhibitory interneurons within the target M1 [40,41]. Another form of measuring interhemispheric inhibition is the ipsilateral CSP, evidenced as the suppression of voluntary EMG activity in one muscle via ipsilateral M1 stimulation [39,42-44]. While both IHI_{10} and ipsilateral CSP are forms of transcallosal inhibition, they are likely mediated by different subsets of transcallosal neurons and different interactions with local inhibitory circuits as evidenced by the lack of correlation in input/output curves between the two measures. Also, the current direction of the CS influences the level of ipsilateral CSP induced, unlike IHI_{10} [44,45]. While both can be considered complementary measurements, ipsilateral CSP can be especially useful in stroke patients who may not have measurable MEPs in the paretic limb after stimulation of the ipsilesional M1, but can produce voluntary EMG activity. Measures of ipsilateral CSP in the paretic limb can reveal the level of transcallosal inhibition targeting ipsilesional M1 [46].

Inter-regional interactions—Paired pulse and rTMS methods have also been used to evaluate the influence of non-primary motor areas within the same and opposite hemispheres on M1, including dorsal premotor (PMd)[47-53], supplementary motor (SMA)[47,54], parietal [55], and cerebellar areas [56-60].

Motor mapping—A cortical map of a target muscle's representation can be rendered by measuring MEP amplitudes evoked in that target muscle by TMS applied to different scalp positions [61-64]; by weighting each point by some measure of the overall map, a center of gravity for a particular muscle representation can also be determined. Motor mapping using TMS has some similarities with mapping using functional neuroimaging in that the size of the map depends to some extent on the intensity of stimulation used and in that an increase in map size may be due to either increased excitability of an unchanged cortical representation or of an actual centrifugal increase in motor map size [65]. Alternatively, motor maps may show well characterized topographic displacement of the center of gravity, as for example what occurs after amputation, where a nearby representation expands consistently over the deafferented representation [66], indicating real representational plasticity.

Central motor conduction (CMC)—The latency of MEP onsets can be used to measure nervous system conduction time. When peripheral conduction time is also known, via magnetic stimulation of the cervical roots or F-wave testing, then a central motor conduction time can be calculated [67,68]. Abnormalities in central motor conduction time may be due to axonal or demyelinating lesions of the corticospinal tract.

This brief introduction intended to define some of the most common TMS measurements and their proposed mechanisms as they have been applied across healthy volunteers and post-stroke populations. For a more detailed description of these measurements and their impact on motor control, please refer to more thorough reviews [33]. Overall, these techniques allow detailed analysis at various levels of interactions within and across cortical areas in health and disease.

Contribution of TMS to the study of stroke rehabilitation

Diagnostic

One area in which TMS has contributed to the neurobiological basis of motor disorders has been when considering the evaluation and diagnosis of psychogenic paralysis. TMS may play a role by identifying normal MEPs and CMC, ruling out corticospinal tract neurophysiological damage [69], and in investigating the nervous system mechanisms behind motor conversion disorder[70]. Liepert et al reported the existence of decreased excitability during motor imagery in patients with this psychogenic paralysis. Such a finding may result in more objective diagnostic criteria for this disorder. Theoretically, a thorough characterization of neurophysiologic abnormalities in this disorder may lead to interventions targeting those abnormalities, and hence better treatment.

Prognostic

One of the major concerns in stroke rehabilitation is prognosis. Previous work demonstrated that high motor thresholds or a complete absence of MEPs in the paretic hand after subacute stroke are associated with poorer prognosis in terms of motor recovery [71-73]. On the other hand, the presence of MEPs, even with prolonged CMC time, may predict better prognosis [72-78]. Functional measurements of corticospinal integrity as provided by TMS can complement data on anatomical integrity as measured by diffusion tensor imaging (DTI). A recent report showed that, consistent with the previous literature, paretic limb MEP presence predicted meaningful gains in chronic stroke patients receiving motor rehabilitation [79]. Within the subgroup of patients in whom MEPs could not be evoked in the paretic hand (theoretically predicting poor prognosis), functional outcome was poorer in patients with greater posterior internal capsule fiber disruption, as measured by DTI. Using these methods together can fine tune our ability to generate more accurate prognostic evaluations [79]

Understanding mechanisms of motor deficits

Using TMS as a complex probe into the neurophysiologic underpinnings of motor function allows researchers to comment about specific mechanisms of behavior and plasticity. Application of these techniques to patients with impaired nervous system will likely reveal more regarding the mechanisms of both injury and recovery after stroke. These measures have potential not only to improve diagnosis and prognosis, as discussed above, but even more intriguingly, to reveal new unpredicted targets for therapy.

Primary motor cortex—One of the early intriguing findings in the application of TMS to stroke patients was the presence of ipsilateral MEPs within the paretic limb [71,80-84], which are otherwise rarely found in healthy subjects at rest. This also seemed to correlate with other measures of increased excitability in the contralesional M1 [85-87]. Interestingly, ipsilateral MEPs have been reported more frequently in poorly recovered stroke patients [71], a finding

interpreted as indicating that contralesional facilitation of excitability may not be a marker of good recovery [80]. Based on these reports, much interest was triggered regarding to what extent alterations in excitability in contralesional M1 influence recovery of motor function in the paretic arm, and what mechanisms may be involved. In subacute severely paretic stroke patients, Liepert et al reported decreased SICI in contralesional M1 as compared to age-matched controls [88]; a finding subsequently replicated in more acute patients [36,89-92]. Also, decreases in SICI in ipsilesional M1 have been consistently reported in the literature, both in the acute and chronic periods after stroke [37,90,93-95]. When assessing changes longitudinally, it does seem that acute disinhibition may, especially contralesionally, normalize over time [92,96]. However, how measures of intracortical inhibition or its changes correlate with function at any particular time-point may be highly dependent on initial patient characteristics [36,92,96]. Another issue that is presently under investigation is the extent to which decreased inhibition in contralesional M1 is present in patients with both cortical and subcortical lesions [36,91], perhaps explaining the relative variance in reproducibility [94, 95]. Finally, intense scrutiny is necessary to determine how these electrophysiological abnormalities relate to previously reported abnormalities in metabolic activity of both the ipsilesional and contralesional hemisphere of patients with stroke [97-104].

Beyond investigation of the local changes in excitability of both M1s in stroke patients, it should be kept in mind that functional recovery is likely related to changes in distributed neuronal networks rather than in individual regions. Studies have begun to investigate the alteration in transcallosal neurophysiology after stroke. IHI_{10} between the two M1s is likely altered after stroke, possibly in a lesion-location dependent manner [105]. Examining whether changes in IHI_{10} and SICI after stroke may be related, Butefisch and colleagues have shown that the attenuation of SICI in ipsilesional M1 is not accompanied by a change in resting IHI_{10} from contralesional to ipsilesional M1. In contrast, disinhibition of contralesional M1 is accompanied but not completely correlated with a decrease in IHI_{10} from ipsilesional to contralesional M1s [37]. Together, these findings may imply that at rest, local modulation of inhibition within ipsilesional M1 is prominent. However, a thorough investigation of the resting interactions between SICI and IHI_{10}, which has begun in healthy individuals [40,106], will need to be carried in stroke patients, at various time points and levels of recovery, before more fundamental conclusions can be made. It should also be kept in mind that neurophysiological abnormalities may be more prominent when patients intend to use the paretic hand, rather than when they remain at rest.

Much of these basic cortical physiology measures have been most thoroughly examined at rest. Clearly, extending such measures to active behavior will add significant insight into post-stroke mechanisms of paralysis. For example, the phenomenon of facilitation of M1 excitability by forceful or complex activity of the ipsilateral limb has been explored in the healthy brain [106-111]. How modulations in SICI & IHI_{10} and their interactions may contribute to this facilitation has also been investigated in healthy subjects [106]. Understanding of these interactions in stroke patients would raise the possibility that non-paretic limb activity could change the physiology of the ipsilesional M1, as proposed in neurorehabilitative interventions like bilateral arm training [112] or mirror therapy [113]. However, with isometric force production, non-paretic arm activity in stroke patients does not lead to as much ipsilateral M1 facilitation as seen in healthy controls [114,115]. Perhaps this lack of task-dependent modulation in ipsilesional M1 is due to abnormalities in IHI_{10} after stroke [116]. Studies have begun to address this question by looking at premovement IHI_{10}. In chronic, relatively well recovered stroke patients, initially normal levels of IHI_{10} from the contralesional to the ipsilesional M1 remain abnormally deep at the onset of paretic hand movement, in contrast to the disinhibition that accompanies non-paretic hand movement and movement in age matched controls [117,118] during a simple reaction time task (Figure 1).

Expanding this line of research to encompass measures of both local and transcallosal neurophysiology and apply them to different motor tasks will allow us to more broadly characterize the neurophysiologic underpinnings of motor deficits after stroke. Clearly, more work is required to fully elaborate these findings.

Non-primary motor regions—Understanding that recovery processes are likely to rely on changes in neurophysiological interactions between different nodes in distributed networks led to the investigations of specific interregional interactions. Investigation of premotor cortex contributions to stroke recovery using TMS have revealed a role for both ipsilesional [119] and contralesional [103] dorsal premotor cortices to the functioning of the paretic hand after stroke, with a trend towards contralesional PMd contributing more effectively in patients with more marked impairment, while ipsilesional PMd could be more active in patients with lesser impairment. A prominent possibility for translation of these findings will be investigations into how purposeful modulation of premotor cortical excitability may influence functional recovery after stroke.

It should be kept in mind that identification of neurophysiological abnormalities in patients with stroke is not an easy task. There are technical challenges, as well as a marked heterogeneity in patients' characteristics that makes generalizations risky. For these reasons, careful manipulation of the various technical tools available is of the utmost importance. It is expected that these new investigations, many presently under way, will in the future allow greater generalizability by fleshing out the details regarding each technique and each subgroup of patients to which they are applied.

Understanding mechanisms underlying the beneficial effects of intervention and therapy

Just as TMS measurements can be used to investigate pathophysiology, they can also be used to gain insight into the mechanisms underlying the beneficial effects of therapeutic interventions. For example, using TMS measures of local inhibition and non-concurrent functional magnetic resonance imaging (fMRI), Hamzei and colleagues demonstrated in chronic subcortical stroke patients that functional improvement from constraint-induced (CI) therapy was accompanied by decreased fMRI activity and decreased SICI in the ipsilesional M1, while the opposite effects were found in patients with lesions in M1 or the corticospinal tract [120]. This study suggested that the beneficial effects of CI therapy might be mediated at least partially by modulation of intracortical inhibition within ipsilesional M1, perhaps accompanied by some level of morphological changes as well[121]. We now know that the benefits of a single session of reaching practice in moderately impaired chronic stroke patients is accompanied by decreased transcallosal inhibition (ipsilateral CSP) [46] only in the trained muscles, implying a specific and differential change in physiology that may contribute to the behavioral gains.

Attempts to enhance rehabilitation by application of different forms of non-invasive electrical and magnetic stimulation to the nervous system have increased [122-125]. Interestingly, TMS can be used not only to carry out the stimulation, but to investigate the mechanisms by which it may be having its effects. For example, it was found that the beneficial effects of applying anodal transcranial direct current stimulation (tDCS) to ipsilesional M1 correlated with a decrease in SICI in this same cortical area [126]. Using an alternative approach, it has been proposed that the beneficial effects of downregulating excitability in the contralesional M1 by cathodal tDCS are associated with a normalization in the abnormal IHI_{10} from the contralesional to the ipsilesional M1 (Hummel et al, unpublished observations), perhaps contributing to clinically significant effects [127-130].

TMS has also been used to evaluate the mechanisms underlying the beneficial effects of somatosensory input modulation in patients with chronic stroke. Specifically, it has been

reported that the beneficial effects on paretic hand motor function caused by cutaneous anesthesia of the non-paretic hand are associated with decreased IHI_{10} from contralesional to ipsilesional M1, which may be an underlying mechanism of action of the post-stroke functional improvements seen with this and similar methods targeting the non-paretic limb, like limb immobilization [131]. When applying somatosensory stimulation to a paretic hand in an attempt to facilitate motor function[132-134], it was found that better baseline motor function was correlated with deeper SICI in the contralesional hemisphere[135]. Also behavioral gains in motor function induced by somatosensory stimulation of the paretic hand were accompanied by a reduction in SICI and SICF in the ipsilesional M1 in patients with chronic stroke [134].

As examination of the physiologic mechanisms underlying the beneficial effects of therapeutic interventions has expanded, so has the desire to use such measures as surrogate markers [136,137]. While changes in TMS measured cortical excitability and motor maps can be seen after various forms of neurorehabilitative treatments [138-145], and correlations can be found with various functional measures, there are significant hurdles to be managed before these measures become useful in the clinical setting. Particularly, all of these measures need to be better standardized to make them consistent and easily reproducible across laboratories [146]. Such standardization would be an important step towards developing these measurements as useful markers of recovery.

Finally, one of the most sought out applications of TMS, as well as other noninvasive stimulation techniques like tDCS, is as an adjuvant strategy for rehabilitation of both motor [123]and cognitive [147] impairment after stroke, an issue that has been thoroughly reviewed recently in this journal [148].

Conclusions and future

While we have summarized the several ways in which TMS can be used to gain insight into the physiological mechanisms underlying motor deficits and neurorehabilitation after stroke, it is clear that one technique alone cannot provide a full mechanistic picture of such a multifaceted problem. Combinations of TMS with other techniques are bound to lead to a more sophisticated understanding. For instance, brain-derived-neurotrophic-factor (BDNF) has been implicated as an important biochemical modulator of neural plasticity[149], and its relationship to physiology as measured by brain stimulation is beginning to be investigated[150-152], although much less is known in terms of its relation to motor learning. It is also being appreciated that in vitro and non-human investigations of nervous system stimulation and physiology have great potential to elucidate some of the complexities that cannot be approached through human TMS work [153,154]. Finally, though it has yet to be applied to stroke patients, concurrent TMS with various forms of metabolic functional imaging [155-157] and other neurophysiologic measures [158] has potential to further elucidate changes in network connectivity after stroke and during rehabilitation. In summary, TMS represents a unique tool for probing the sophisticated physiologic mechanisms underlying motor and non-motor network activity mediating normal and impaired behavior after stroke and other brain lesions. And from a more sophisticated understanding of the underlying physiology, so will come more sophisticated and effective interventions.

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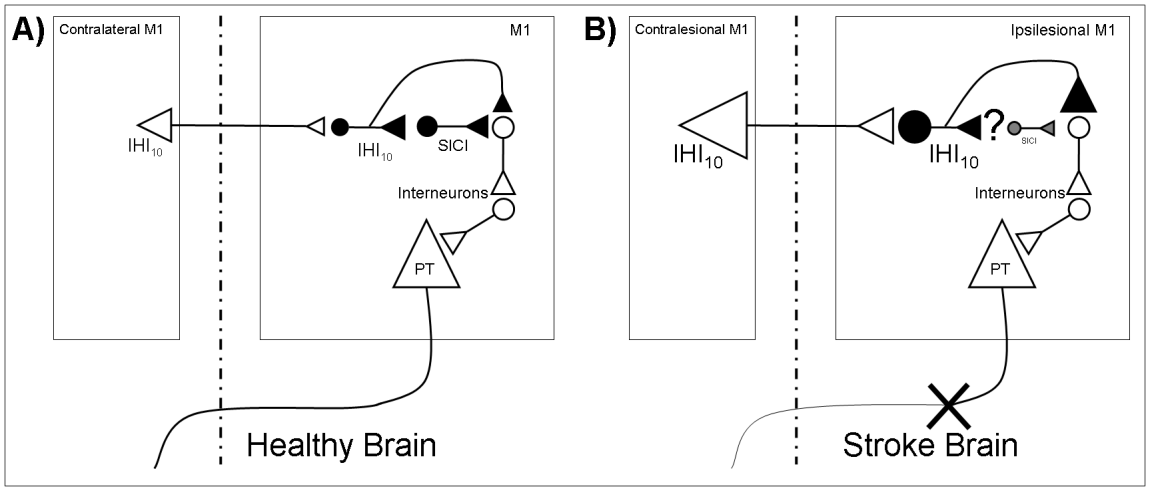

Figure 1. Intra- and inter-hemispheric excitability within M1 in the healthy (A) and stroke affected (B) brain

This diagram depicts intracortical neuronal populations within the primary motor cortices that experience excitability changes after stroke. Black neurons reflect inhibitory influences and white neurons represent excitatory populations. A) Diagram of M1s interactions in the healthy brain that result in modulation of excitability in pyramidal tract (PT) neurons as tested by TMS. B) Changes in activity of these networks after stroke. Ipsilesional short interval intracortical inhibition (SICI) within M1 is decreased compared to the contralesional M1. At movement onset, interhemispheric inhibition at 10ms inter-stimulus intervals (IHI_{10}) from contralesional to ipsilesional M1 is greater in the stroke brain than in the healthy brain. Whether this change in IHI_{10} is due to an increase in the transcallosal glutamatergic elements or ipsilesional inhibitory networks, and how IHI_{10} interacts with SICI in the stroke brain have yet to be elucidated.