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Transcranial magnetic stimulation for the prediction and enhancement of rehabilitation treatment effects

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Abstract

In this update on rehabilitation technology, transcranial magnetic stimulation (TMS), a technique that allows non-invasive stimulation of the brain, is examined. The background and basic principles of TMS are reviewed and its usefulness as a tool to inform and possibly augment the rehabilitation process is discussed. The 3 main paradigms by which TMS is applied, 1) physiological measurement, 2) disruption/virtual lesion studies and 3) modulation of cortical excitability, are discussed relative to the types of scientific information each paradigm can provide and their potential clinical usefulness in the future. One of the more exciting prospects is that, when combined with rehabilitation training, TMS modulation of cortical excitability could potentially enhance the effects of rehabilitation and lead to greater levels of recovery than are currently attainable with rehabilitation alone. It is concluded that current studies must focus on the mechanisms of recovery based on the specific structures and processes affected by the disorder and the neural effects of specific rehabilitation interventions in order for the potential of TMS-augmented rehabilitation to be realized.

Background

As the capabilities and availability of technologies expand, their possible applications to rehabilitation seem to expand as well. One such technology is transcranial magnetic stimulation (TMS), a technique that allows non-invasive and painless stimulation of the surface of the brain. The following provides an overview of the current investigational uses of TMS, as well as some speculation regarding the clinical applications that could emerge. The discussion and examples are drawn primarily from work related to motor recovery of the upper extremity after stroke, partly because of author expertise, but primarily because the volume of research in this area exceeds that of other neurological conditions and impairments (for a recent review see Bashir et al 2010 and Hoyer & Celnik 2011).^{1,2}

The idea of stimulating the brain to study cortical function and to treat brain disorders is not new. Penfield and colleagues discovered the somatotopic organization of the human primary motor cortex (M1) by directly stimulating the brains of patients who were undergoing surgery.³ In an attempt to stimulate the brain non-invasively, transcranial electrical stimulation was developed.⁴ However, because of the high electrical resistance of the tissues overlying the brain, high intensities are needed to stimulate the cortex and the stimulation is therefore quite noxious. The discomfort caused by such high levels of stimulation made this technique impractical for widespread use in humans.

In 1985, Anthony Barker and colleagues⁵ introduced a different way of using electrical currents to stimulate the brain. Instead of focusing the electrical current directly into the scalp, the current runs tangential to the scalp. As may be recalled from a long-ago physics class, when an electrical current travels through a wire, it creates a magnetic field with a direction perpendicular to the direction of the current (Figure 1A). This is known as Faraday's Law of electromagnetic induction. Importantly, the reverse is also true. A magnetic field with a particular direction creates a small perpendicular electrical current. Unlike electrical currents, magnetic fields pass through the scalp and cranium relatively unimpeded. In this way, the magnetic field acts as a "carrier" of the electrical current needed to stimulate the underlying neurons (Figure 1B). Because the cranium and surrounding tissues have lower impedance to a magnetic field, this stimulation is much more tolerable than electrical stimulation and is considered painless by most people who have experienced it. For a complete discussion of the electro-dynamics of TMS, please see Pascual-Leone et al., 1999 and Hallett 2000, 2007.^{6,7,8}

The introduction of this tool truly represented a break-through for the study of human brain function. For the first time, scientists could stimulate the brain in fully awake, un-anesthetized, behaving (e.g. performing a cognitive or motor task) humans, and measure the effects. It is a flexible tool, as well. It has been used to study the roles of particular brain areas in domains such as language, learning and memory, vision, and of course, movement. It is fortunate for those with an interest in motor recovery that many motor system structures lie on the surface of the brain and are thus accessible with TMS.*

The Double-Edged Sword of Plasticity

In order to understand how best to use a particular tool, it is important to consider what it is we are trying to achieve. In order to effectively use the tool of TMS, it is crucial to understand which brain areas' activation contributes to neural recovery and which areas' activation could actually deter recovery. For example, it is well known that there is wide variability in the levels of recovery attained after apparently similar strokes and similar levels of initial impairment. We know that the motor system is capable of remarkable reorganization, so what happened in the motor networks of those who recovered that did not happen in those who did not? Specifically, which areas are active in people with better arm recovery? The reverse is also important: which areas are active in people with poorer arm recovery? This raises the key problem at the moment: the double-edged sword of plasticity. Remarkable brain reorganization can take place after a stroke or other brain injury, but some of this reorganization appears to be maladaptive, potentially further contributing to the resulting disability.^{10,11,12} If beneficial vs. maladaptive brain activations could be accurately identified and their roles understood in the context of different lesion locations and clinical presentations, non-invasive cortical stimulation techniques could enhance the efficacy of rehabilitation treatments and the resulting recovery beyond what is currently attainable; obviously a very exciting proposition.

A variety of non-invasive methods have emerged for increasing (up-regulating) or decreasing (down-regulating) cortical excitability in the brain, some of them more focal than others. TMS, in fact, is a tool commonly used for this purpose, as will be discussed in more detail below. Such techniques could be used to strategically up- or down-regulate cortical excitability in specific brain areas before or during motor practice, potentially enhancing the effects of practice and, ultimately, motor recovery. Some investigation into this possibility has already begun, and is discussed below. However, we still know relatively little about the

*Estimates of the maximal depth of TMS effects vary and are dependent on many factors, but are generally agreed to be in the range of 2–2.5 cm.⁹

roles of and interactions between different brain areas after different kinds of strokes; information that is vital in order for the potential of non-invasive brain stimulation to be realized at the clinical level.

In the following sections, 3 general approaches to the use of TMS in the motor system will be discussed: physiological measurement, instantaneous disruption, and modulation of cortical excitability. Each section will include 1) examples of how the technique is currently being used to unravel the questions outlined above and 2) how it could be used clinically in the future when more information on recovery mechanisms is available.

Physiological Measurement

Unlike other systems such as language and memory, the motor system allows us to not only measure the effects of TMS on behavior, but also the brain physiology associated with that behavior. This is because we can measure the effect of brain stimulation at the target of the area we are stimulating; namely, muscles.^{7,8,13} These measurements can be made using surface electromyography (EMG) placed over the muscle of interest (Figure 1C). When the M1 area associated with the muscle is stimulated using TMS, its neuronal pool is activated, resulting in action potentials which travel down the corticospinal tract to the final common pathway and the innervated muscle. Often, the stimulus is strong enough that it causes a visible muscle twitch. Even when no twitch is observed, the facilitation at the muscle can be recorded using surface EMG. The recorded response is known as a motor evoked potential (MEP; Figure 1D). The latency and amplitude of the MEP give us information about the integrity and excitability of the corticospinal system. Many other aspects of motor system physiology can be measured using TMS, including the strength of intracortical inhibition within M1 and the strength of interhemispheric inhibition between opposite motor cortices. A full discussion of the physiological measurements that can currently be made with TMS is outside the scope of this paper and has been described nicely elsewhere.^{7,14,15,16} Instead, examples of the potential clinical usefulness of a simple MEP measurement will be offered.

As alluded to above, the MEP from a particular muscle can tell us something about the integrity of the corticospinal pathway which serves that muscle. For example, if the muscle cannot be voluntarily activated, but an MEP is easily evoked, this would indicate that at least some of the crossed corticospinal tracts have been spared. In such a scenario, the clinician might consider a treatment plan aimed at recovering voluntary activation and control of that muscle. On the other hand, those in whom no MEP can be elicited may be better served by more compensatory training.

Another potential role of physiological testing in rehabilitation is predicting which treatment approaches might be most effective in a given individual. It has been shown that TMS can detect neurophysiological changes after a single session of motor practice, even in severely hemiparetic stroke patients.¹⁷ Importantly, Koski et al.¹⁸ measured the asymmetry in MEP amplitude between the affected and less affected hands in stroke patients entering rehabilitation therapy focused on repetitive goal-oriented task practice. They found that the change in MEP amplitude asymmetry after a single session of therapy predicted the overall behavioral improvement after an average of 4 weeks of treatment.

One could imagine future rehabilitation clinicians using this type of simple physiological testing performed immediately before and after a single session of a particular treatment approach. The change in MEP amplitude after a single session of one treatment could be compared to that observed after other possible approaches to determine which seem to have the greatest effect on the motor system of that individual. This type of clinical information could prove invaluable in individualizing treatment plans and improving the efficiency of rehabilitation by not spending time and resources on treatments that are less than optimal.

Disruption

Another way to gain important rehabilitation-relevant information using TMS is through so-called disruption or “virtual lesion” studies.^{6,7,8,19} In these types of studies, instead of a physiological measurement, as described above, *behavioral* measurements of task performance or learning are made. If TMS to a particular brain area changes the observed behavior, it can be assumed that the stimulated area is part of the network that controls that behavior.

Virtual lesion studies are performed either as an instantaneous disruption or as a more sustained suppression of excitability. The former is most often carried out in the context of a reaction time task. The study participant is asked to perform a cognitive or behavioral task in response to a visual or auditory “Go” signal. Reaction time is most often defined as the duration between the “Go” signal and the onset of EMG activity (Figure 2A). In an investigation of brain areas supporting finger movements after stroke, Fridman et al.²⁰ asked participants to press a button with their affected hand as quickly as possible after a “Go” signal. In half of the trials, a TMS pulse was delivered 120 msec after the “Go” signal to instantaneously disrupt either the contralateral M1, or ventral or dorsal premotor cortex (PMd). A delay in reaction time in stimulation trials provides evidence that the stimulated area was involved in movement planning at the moment it was disrupted and its disruption led to the delay in movement onset. In healthy controls, stimulation of M1 120 msec after the Go signal resulted in a delay in contralateral hand reaction time, but stimulation of PMd at the same time point did not (Figure 2B). In the *non-lesioned* hemisphere of stroke patients, a similar pattern was observed: stimulation of M1 in the non-lesioned hemisphere resulted in delayed less-affected hand reaction time, but stimulation of PMd did not (Figure 2C). However, unlike PMd disruption in healthy volunteers and the non-lesioned hemisphere of stroke patients, stimulation of the *lesioned* hemisphere PMd in stroke patients resulted in marked delays in reaction time of the stroke-affected hand (Figure 2D). Thus, it appears that the lesioned hemisphere PMd may have taken on a functional role in the lesioned hemisphere that it does not have in the non-lesioned hemisphere of stroke patients or in healthy volunteers. This is the type of information that is needed to make inferences regarding where to target interventions that can directly modulate cortical excitability.

In the future, this kind of method could potentially be used to guide clinical decision-making as to which brain areas to modulate before rehabilitation therapies are performed. It could provide information that is specific both to the individual and the type of task that will be targeted in the subsequent rehabilitation session. For example, if proximal arm tasks such as reaching are going to be trained, a reaching task in response to a “Go” signal could be used. A TMS pulse could be delivered just after the Go signal to different candidate brain areas to determine the effect on reaction time or some other measurement of task performance. If a decrement in task performance is observed, it would be concluded that the stimulated area was contributing to task performance. It is also possible that disruption of certain brain areas could result in enhanced performance, in which case it would be concluded that activation in that area was perhaps excessive and maladaptive

Modulation

TMS can be used not only to measure cortical physiology or produce instantaneous disruption that is time-locked to a specific task, but it can also produce longer-lasting modulation of cortical excitability.^{6,14,21} This is done by applying a train of TMS pulses, called repetitive TMS (rTMS), usually while the individual is at rest (i.e. not performing any specific task). Cortical excitability can be either up- or down-regulated depending on the

frequency and pattern with which the pulses are delivered. The resulting modulation of cortical excitability persists for a period of time after the end of the stimulation period.

Various applications of rTMS have been associated with improved motor performance, learning, and consolidation in both healthy individuals and individuals with stroke (for review see Censor and Cohen 2011).²² Key factors under active investigation include the location (e.g. affected vs. unaffected hemisphere in stroke; primary vs. non-primary motor areas), timing (e.g. before, during or after motor practice) and the pattern and frequency of pulse delivery. For example, in healthy individuals, application of excitatory rTMS over the contralateral PMd before motor practice resulted in enhanced consolidation of motor learning in the right arm.²³ Interestingly, *inhibitory* rTMS over the M1 ipsilateral to the moving hand can also result in improved motor performance and learning.^{24,25} This effect has lent support to an important conceptual hypothesis that is driving current inquiry in the field: interhemispheric competition.^{26,27} We know that, in the healthy brain, the effects of the interactions between the left and right M1 via the corpus callosum are primarily inhibitory. Therefore, in the context of motor tasks, down-regulation of the ipsilateral hemisphere via inhibitory rTMS could result in a release of interhemispheric inhibition targeting the active hemisphere and possibly improve motor performance and learning. Indeed, inhibitory rTMS applied to one hemisphere has been shown to result in increased excitability of the contralateral hemisphere in healthy humans.²⁸

Similarly, based on the interhemispheric competition hypothesis, a stroke in one hemisphere could result in a release of that inhibition over the contralateral, non-lesioned hemisphere. The non-lesioned hemisphere, then, is disinhibited and could become hyper-excitabile, in turn producing excessive inhibition of the lesioned hemisphere. This idea has provided the rationale for interventions aimed at decreasing non-lesioned and increasing lesioned hemisphere excitability, as discussed below. Perhaps more importantly, it has solidified the idea that stroke-related impairments may be due not only to the lesion itself, but also to the changes induced in other brain areas that have disrupted connections to the lesioned area.

Based on the idea of unbalanced excitability between the lesioned and non-lesioned hemisphere, rTMS techniques have been used to investigate the effects of decreasing excitability of the non-lesioned hemisphere M1 and enhancing excitability of the lesioned hemisphere M1, often in conjunction with physical practice. Inhibitory rTMS to the contralesional M1 can result in improved motor performance of the affected hand,^{29,30,31,32,33} with larger effects observed after multi-day treatments.³¹ Importantly, inhibitory rTMS to the contralesional M1 can also enhance practice-induced improvements in motor performance of the affected arm,^{33,34} and may have an effect even in patients with severe motor impairments.³⁵ The reverse approach, application of excitatory rTMS to the ipsilesional hemisphere, has been shown to improve hand motor performance in patients with subcortical lesions³⁶ and to enhance practice-induced improvements in motor performance.^{37,38} However, this effect is not always observed,³⁹ for reasons that are not yet fully understood. Thus far, the sample sizes in these studies have been relatively small and the results, while promising, are not dramatic and are quite variable. However, it is likely that as we gain a better ability to individualize treatments based on pathological and clinical considerations, larger recovery effects will be observed.

Given the preceding discussion, possible future applications of non-invasive modulation of cortical excitability using TMS in the clinical setting are clear.⁴⁰ However, it is important to consider the feasibility of applying this technique in the clinical setting. In some clinical settings, TMS is already being used to perform electrophysiological assessments, such as central conduction time, for diagnostic purposes. These kinds of assessments require a relatively simple stimulator capable of delivering a single pulse every 8–10 seconds. For

more complex paired-pulse measurements, two such stimulators are needed. If the goal is not just to measure, but to *modulate* cortical excitability, a more complex stimulator that can deliver repetitive TMS pulses at a minimum of 1 Hz frequency is required. Repetitive TMS has already been approved by the Food and Drug Administration (FDA) for the treatment of depression and it is being used clinically for this purpose. To translate this to rehabilitation, a repetitive TMS treatment room could conceivably be located in or near the rehabilitation area so that rTMS could be applied by a trained technician just prior to rehabilitation sessions. Relative to other medical diagnostic and interventional devices, TMS devices are inexpensive and, as indicated above, they are already being used for electro-diagnostics and to treat depression in many hospitals and clinics. It is therefore not outside the realm of possibility to imagine diagnostic and interventional TMS being used to guide and enhance rehabilitation in the future.

Summary

TMS is an extremely flexible tool that can serve a number of different scientific and, perhaps in the future, clinical purposes. It can be used to examine cortical physiology, particularly that of M1. Using surface EMG over the muscles of interest to measure the responses, it can provide measurements of corticospinal tract integrity, as well as the strength of interactions within the brain itself, such as intracortical and interhemispheric inhibition. In addition, TMS can be used to instantaneously disrupt a particular brain area to investigate the role of that area in the resulting behavior. As we try to understand the possible roles of maladaptive vs. beneficial plasticity, this technique could be useful. If the behavior is disrupted with stimulation, it can be assumed that the stimulated area was contributing to the task performance; if behavior is enhanced, the stimulated area could be interfering with task performance. Such an approach could be used to drive clinical decision-making in the future; including decisions regarding the subsequent use of rTMS to modulate cortical excitability. Repetitive TMS pulses, given at various frequencies and in different patterns, can either increase or decrease cortical excitability. This property has already been harnessed in the clinical treatment of depression with encouraging results. It is hoped that future work will provide the evidence necessary for these techniques to support the rehabilitation process and enhance recovery levels in patients with neurological disorders.

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TMS Localization Where to place the stimulating coil?

When targeting primary motor cortex (M1), the size of motor evoked potentials (MEPs) recorded by electrodes placed over the muscles of interest is used to determine optimal coil placement. “Scouting” is often performed, in which the coil is moved over the scalp in small increments around the expected M1 location until the position that consistently produces the largest MEPs, often called the “hotspot,” is determined. The outline of the coil is then traced onto a close-fitting cap on the participant’s head to ensure that the coil is kept in the same place throughout the testing.

When investigators began targeting non-primary motor areas, this approach became more problematic since MEPs could not be used to confirm correct coil localization. Initially, these areas were targeted based on their average distance from the motor “hotspot”. For example, for targeting the dorsal premotor cortex, the coil position would often be 2 cm anterior and 1 cm medial to the motor hotspot. Obviously, differences in head size and shape make this approach sub-optimal. A better approach is stereotactic neuro-navigation, in which a high-resolution MRI of the participant’s brain is used to guide and record coil location. This approach uses simple motion tracking technology to display the location of the coil relative to the participant’s head and, via 3-dimensional reconstruction of their MRI data, the underlying neuroanatomy. This provides a much more accurate, repeatable, and individualized approach to coil localization, particularly when targeting non-primary motor areas.

Figure 1.

This figure illustrates the use of TMS to elicit a motor evoked potential from a forearm muscle. **A)** When an electrical current (I) runs through a wire, it sets up a magnetic field (B) with a direction perpendicular to the wire. **B)** When a current is run through the wires of a TMS coil, the resulting magnetic field passes through the skull and produces an electric current in the brain. **C)** Non-invasive surface electrodes can be used to record the response to stimulation of the motor cortex. **D)** This reading from a surface electrode shows some low-level activation of the muscle followed by a large spike in activity a few milliseconds after the TMS stimulus. This spike is called a motor evoked potential (MEP).

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Figure 2.

TMS disruption studies are usually performed in the context of a reaction time task. **A** Schematic of a disruption study. The TMS pulse is delivered 120 msec after the “Go” signal and the effect on reaction time (the time from the “Go” signal until the onset of EMG activity) is measured. The effect of either sham (no stimulation delivered) or real TMS to primary motor cortex (M1) or dorsal premotor cortex (PMd) is shown in a healthy volunteer (**B**), and a stroke patient’s non-lesioned (**C**) and lesioned (**D**) hemisphere. Note that PMd stimulation does not induce a reaction time delay in the healthy volunteer or the stroke patient’s non-lesioned hemisphere, but it induces a marked reaction time delay when applied to the patient’s lesioned hemisphere. Adapted from Fridman et al., 2004.²⁰

[Fridman EA, Hanakawa T, Chung M, Hummel F, Leiguarda RC, Cohen LG. Reorganization of the human ipsilesional premotor cortex after stroke. *Brain*. 2004 Apr; 127(Pt 4):747–58, by permission of Oxford University Press.]