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Enhancement of human cognitive performance using transcranial magnetic stimulation (TMS)

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Abstract

Here we review the usefulness of transcranial magnetic stimulation (TMS) in modulating cortical networks in ways that might produce performance enhancements in healthy human subjects. To date over sixty studies have reported significant improvements in speed and accuracy in a variety of tasks involving perceptual, motor, and executive processing. Two basic categories of enhancement mechanisms are suggested by this literature: direct modulation of a cortical region or network that leads to more efficient processing, and addition-by-subtraction, which is disruption of processing which competes or distracts from task performance. Potential applications of TMS cognitive enhancement, including research into cortical function, rehabilitation therapy in neurological and psychiatric illness, and accelerated skill acquisition in healthy individuals are discussed, as are methods of optimizing the magnitude and duration of TMS-induced performance enhancement, such as improvement of targeting through further integration of brain imaging with TMS. One technique, combining multiple sessions of TMS with concurrent TMS/task performance to induce Hebbian-like learning, appears to be promising for prolonging enhancement effects. While further refinements in the application of TMS to cognitive enhancement can still be made, and questions remain regarding the mechanisms underlying the observed effects, this appears to be a fruitful area of investigation that may shed light on the basic mechanisms of cognitive function and their therapeutic modulation.

Keywords

Transcranial Magnetic Stimulation; TMS; enhancement; facilitation; cognitive performance

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Introduction

Cognitive enhancement can be defined as any augmentation of core information processing systems in the brain, including the mechanisms underlying perception, attention, conceptualization, memory, reasoning and motor performance (Sandburg and Bostrom, 2009). As Sandburg and Bostrom point out, physiological approaches towards cognitive enhancement have tended towards pharmaceutical research. However, this review will suggest that non-invasive brain stimulation, specifically transcranial magnetic stimulation (TMS), may be a promising alternative. TMS uses very brief high intensity magnetic fields to induce currents and thus depolarize neurons in small regions of cortex. The neural effects of TMS depend on the frequency of stimulation. When the frequency of TMS stimulation is 1Hz or greater, the stimulation is called repetitive TMS (rTMS). If rTMS is pulsed at a low frequency (about 1Hz), cortical excitability generally decreases, while higher frequency rTMS (usually between 5-20Hz) can increase cortical excitability (Pascual-Leone et al., 1994; Chen et al., 1997). This ability to up- or down-regulate cortical excitability, along with its high temporal resolution, suggests that TMS might be a useful tool to manipulate cortical networks in ways that could alter cognitive performance.

Reports of TMS acting to cause cognitive enhancement occurred soon after its introduction as a research tool, with studies observing speeded response in simple reaction time (RT) tasks (Pascual-Leone et al., 1992) and better memory recall (Pascual-Leone et al., 1993; Wassermann et al., 1996), although in the former case the speeded RTs were explained by a general psychological attention effect rather than a specific effect on the stimulated cortex (Tereo et al., 1997), and in the latter cases the effects did not reach statistical significance. Nonetheless, beginning in the late 1990's reports of statistically significant findings of TMS-induced performance enhancements have accumulated.

In the context of cognitive processing, initial reports of facilitated performance were somewhat surprising, as TMS was thought to be a disruptive agent, producing random firing of a population of neurons, generating neural noise that interfered with ongoing processing, thus producing a temporary virtual lesion. Some early studies reporting performance enhancement with TMS suggested a mechanism of “paradoxical” facilitation, in which TMS selectively disrupted the processing of distracting stimulus elements, allowing task-relevant processing occurring at separate locations to proceed more smoothly (e.g., Walsh et al., 1998). In other studies a paradoxical explanation seemed unlikely, as the areas stimulated were thought to be central to the relevant task processing (e.g., Boroojerdi et al., 2001; Grosbras and Paus, 2002). In these cases, TMS may have acted directly on targeted cortex to cause changes that facilitated, rather than disrupted, processing.

While the particular target of stimulation is of course central, whether TMS is disruptive or facilitatory may also depend on other stimulation parameters, such as the frequency, duration, and timing relative to a given task. For example, one form of working memory (WM) task is the delayed-match-to-sample, in which a set of stimulus items are encoded, followed by a delay period, and then a test item which is to be responded to as being a member of the encoded set or not. In an initial finding, a train of 5Hz rTMS applied to dorsolateral prefrontal cortex during the delay period was shown to increase errors in the task (Pascual-Leone and Hallet, 1994). A number of other studies have also demonstrated disruptive effects of TMS in delayed-match-to-sample tasks (Cattaneo et al., 2009a; Desmond et al., 2005; Feredoes et al., 2007; Hamidi et al., 2009a; Herwig et al., 2003; Koch et al., 2005; Mottaghy et al., 2002). When letter stimuli were used as the encoded items, 15Hz trains applied during the delay period to left premotor cortex (Herwig et al., 2003) and 10Hz trains to left temporo-parietal cortex (Feredoes et al., 2007) also decreased accuracy. On the other hand, 5Hz trains applied during the delay period to midline parietal cortex speeded RT without decreasing accuracy (Luber et al., 2007a). In addition, in the Luber et al. study, it was only 5Hz stimulation, and not 1Hz or 20Hz that resulted in performance enhancement. These studies suggest that processing essential to the WM task may occur (and be disrupted by rTMS) during the delay period in left premotor and temporo-parietal cortex, while task-related processing occurs in midline parietal cortex in the test phase of the task, with frequency-specific stimulation prior to that phase aiding processing. Task-phase sensitivity to disruption or enhancement by TMS was also demonstrated in Cattaneo et al. (2009a), where single pulses applied to occipital cortex in the test phase slowed RT, while those applied in the delay phase enhanced RT: TMS in the former condition presumably disrupted processing of the test stimulus, while in the latter condition prior TMS aided processing.

After a search of the literature, we found sixty-one instances of performance enhancement associated with TMS. These included reports of better perceptual discrimination and motor learning, faster eye movements, and speeded visual search and object identification, as well as superior performance on tasks involved in attention, memory, and language. Enhancement has been reported using various TMS paradigms, including single pulse, theta burst, paired pulse, and trains of rTMS at both low and high frequencies. These various forms of TMS are thought to affect cerebral cortex differently, some acutely disrupting processing with the addition of neural noise or briefly inhibiting or facilitating activity, and others modulating cortical excitability up or down for periods beyond the stimulation. As such this suggests that multiple mechanisms are involved with TMS enhancement effects, and our survey suggested that these potential mechanisms could be grouped into three classes: nonspecific effects of TMS, direct modulation of a cortical region or network that leads to more efficient processing, and disruption of competing or distracting processing (i.e., *addition-by-subtraction*). The next three sections discuss these classes. It should be pointed out that the expectation from its beginnings has been that TMS will cause a disruption in processing and performance, and in general the finding of an enhancement has usually been a surprise. The classifications and mechanisms offered in the next sections are an attempt to sort out possibilities behind TMS cognitive enhancement, acknowledging that explanations are still *post hoc* and in the suggestion, rather than prediction, phase.

Enhancement via nonspecific effects of TMS

Better performance in tasks need not be the result of direct influence on cortical processing. TMS also produces a number of superficial effects, including a clicking sound and mechanical vibrations passed from the coil to the scalp. These peripheral auditory and somatosensory sensations can cause a phenomenon called intersensory facilitation (IF: Tereo et al., 1997). Specifically, if the TMS pulse occurs closely in time with the onset of a stimulus to be responded to, speeded RT can result- a purely psychological effect unrelated to the effects of the magnetic field on cortex below the TMS coil. For example, IF was suggested as the cause of enhanced performance in one study of visual motion discrimination (Campana et al., 2003). Here rTMS was applied to primary visual cortex, left extrastriate cortex, right angular gyrus, and vertex, the last being a control site not expected to be affect task performance. At all sites including the vertex, RTs were decreased with TMS compared to no TMS, a non-specific effect attributed to IF.

Using offline rTMS separates the stimulation and performance of the task in time, removing distracting factors, but even here non-specific enhancements still may occur. An example can be found in the results of another study in which TMS sped RT in a picture-word matching task (Drager et al., 2004). Subjects received 10 minutes of 1Hz rTMS at five different scalp locations, and sham stimulation at one of them. In the block of trials immediately following the stimulation RT decreased in all cases, significantly so for three of the sites, as well as for sham. This non-specific effect of TMS was attributed by the authors to general arousal unrelated to the processing specific to the task.

Enhancement mechanisms involved with direct TMS to task-related cortex

This class of mechanism relies on direct interaction of TMS with neural activity in an area needed for task performance. Single TMS pulses occurring immediately before the onset of a stimulus to be responded to have produced performance enhancements (Topper et al., 1998; Grosbras and Paus, 2002; 2003), suggesting the pulse potentiates local neural activity for a brief period. Grosbras and Paus (2002; 2003) found that stimulation delivered 40 ms before the onset of a small target light increased its detectability. They noted that in animal studies direct electrical stimulation of neurons in the same visual area immediately preceding a target improved performance, and that some models of decision making posit that the amount of neural activity in the relevant network can determine whether a stimulus reaches awareness. They suggested that the additional neural activity caused by the TMS pulse may often have brought the neural response to the target stimulus above the threshold of awareness. Short trains of high frequency rTMS also appear to directly facilitate cortical processing. (Gagnon et al., 2011; Kohler et al., 2006; Luber et al., 2007a; Wipfli et al., 2001). A possible mechanism suggested by Berardelli et al. (1998) for this enhancement is post-tetanic facilitation, an increase in excitatory post-synaptic potentials due to trains of electrical stimulation found in animal studies (Iriki et al., 1989).

Another possible mechanism for enhancement due to trains of rTMS is based on neural dynamics. Converging evidence highlights the importance of oscillatory behavior in cortical integration (Crick and Koch, 1990; Schnitzler and Gross, 2005), and in memory, attention and perception (Buzsaki and Draguhn, 2004; Freunberger et al., 2011; Fox and Schroeder, 2005; Lakatos et al., 2005). TMS can reset and drive this oscillatory behavior (Fuggetta et al., 2008; Van Der Werf and Paus, 2006; Thut et al., 2011), and could possibly be used to enhance oscillatory function (Hamidi et al., 2009b). For example, two second trains at individual alpha frequency (IAF) immediately preceding stimulus onset has also increased accuracy in a mental rotation task (Klimesch et al., 2003). Performance enhancements have been found to be frequency-specific (e.g., 10Hz but not 5 or 20Hz in Romei et al., 2010; IAF

+1 but not IAF-3 or 20Hz in Klimesch et al., 2003; 5Hz but not 1 or 20Hz in Luber et al., 2007a), presumably reflecting entrainment of functionally-relevant oscillations. In one interesting application, theta (i.e., 5Hz) and beta (20Hz) frequency rTMS to the same region (right parietal cortex) had differential enhancing effects, depending on whether the subject was to attend global or local aspects of a visual stimulus (Romei et al., 2011). The theta rhythm may work to entrain neural networks across large regions of the brain in the service of memorial and attentional faculties (e.g., Sirotta et al., 2009), and in that regard it is interesting that a number of studies show cognitive enhancements involving executive functions with the use of 5Hz stimulation (Boroojerdi et al., 2001; Cooper et al., 2004; Kohler et al. 2006; Luber et al., 2007a; Romei et al., 2011; Yamanaka et al., 2010). In all, the use of rTMS to modulate neural systems via interaction with their functional oscillations may be quite a promising approach in generating cognitive enhancement.

An offline approach of repeated trains of high frequency stimulation for 10-20 minutes immediately preceding a task has also produced performance enhancements (Boyd et al., 2009; Hwang et al., 2010; Ragert et al., 2003; Tegenthoff et al., 2005). For example, twenty-five 10 s trains of 5Hz rTMS reduced subsequent tactile discrimination thresholds for up to two hours (Tegenthoff et al., 2005). The extension of effects beyond the end of multiple trains of stimulation suggests a mechanism based on long term potentiation (LTP), a temporary change in synaptic plasticity caused by electrical stimulation of hippocampal slices of animals (Bliss and Lomo, 1973; Bliss et al., 2003). LTP-like plasticity effects have been reported using trains of rTMS on motor cortex (Peineman et al., 2004; Touge et al., 2001) and somatosensory cortex (Ragert et al., 2004) by examining changes caused in motor evoked potentials (MEPs). Direct changes in motor cortex excitability ostensibly caused by rTMS-induced LTP have also been observed using topographic EEG (Esser et al., 2006). It should be noted that there is also some evidence that plasticity effects of rTMS may also have to do with modulation of cortical inhibitory systems (Funk and Benali, 2010).

The synaptic effects involved in LTP have long been thought to be related to processes of memory and learning, based on Hebbian notions of changes in synaptic strength via co-activation of input neurons, and such neural co-activation might be facilitated using TMS (Tegenthoff et al., 2005). For example, repeated co-stimulation of the median nerve in the forearm and motor cortex can potentiate subsequent MEPs evoked by TMS (Stefan et al., 2000; Wolters et al., 2003). In an interesting application of these ideas, Butefisch et al. (2004) found that repeated trials applying a TMS pulse to motor cortex simultaneously with a training movement of the thumb enhanced the execution of the movement for more than an hour, while TMS asynchronous to movement did not. Given the activation of Hebbian and LTP-like mechanisms, TMS has the potential to accelerate skill learning, with the key being to target a cortical region essential to the skill or to learning it, and to apply TMS in conjunction with exercise of the skill. The relative timing of TMS with skill performance may be somewhat fluid: as TMS can generate plasticity effects that last beyond the stimulation period, skill performance may occur before, during or after the stimulation period with efficacious results (Thickbroom, 2007). For example, in one study 5Hz rTMS was applied over a 15 min period to motor cortex, followed by a training session in a motor tracking task, resulting in improved motor performance lasting at least one day (Boyd et al., 2009).

Studies reporting performance enhancements with TMS targeting regions expected to be directly involved in a given task are listed in Table 1. TMS can facilitate task performance whether given as a single pulse, a short train of pulses, or offline using multiple trains. Two keys to enhancement appear to be that stimulation be done immediately before performance, potentiating target cortex for task-related processing, and with rTMS, that high frequency rTMS is used, with the particular frequencies chosen based on their potential for interaction with intrinsic functional oscillations. Further, the LTP-like effects of rTMS, and the potential of co-activating targeted cortex with TMS and task performance to result in Hebbian memory effects, suggest the possible use of TMS in enhancement of skill acquisition.

An exception to the first key to TMS enhancement cited above (i.e., stimulate immediately prior to processing) can be found with TMS actually applied during cortical processing via a suggested effect called stochastic resonance (Miniussi et al., 2009). For example, three pulses of 20Hz rTMS were applied in a direction-of-motion discrimination task to area V5 immediately *after* the onset of a visual stimulus, presumably during the time when processing in V5 should be crucial to the task (Schwarzkopf et al., 2011). In conditions when the visual signal was strong (i.e., high coherence in the motion of dots in the same direction), such stimulation at or slightly below the subject's motor threshold lowered accuracy, a performance deficit caused by disruption of ongoing cortical processing important to the task typically seen with TMS. However, in the case of low visual signal coherence, very weak intensity (60% motor threshold) TMS significantly increased accuracy. The authors suggested that a small visual signal often doesn't produce enough neural activity to pass a decision threshold and so is missed; but the neural noise added by the weak TMS pulses, while not enough to overwhelm the visual signal, actually boosts the overall background activity the signal is riding on such that the additional activity created by the signal reaches above the decision threshold, resulting in a successful hit and improved accuracy. This example of stochastic resonance demonstrates the need to model the state of the neural system in interpreting or predicting performance enhancement due to brain stimulation (Silvanto et al., 2008a).

Enhancement via “addition-by-subtraction”

Another class of mechanism by which TMS might produce cognitive enhancement is through disruption of processing which competes or distracts from task performance. This type of mechanism can be thought of as addition-by-subtraction, and can be illustrated by a study of visual search (Walsh et al., 1998). Single pulse TMS applied during stimulus presentation to a superior occipital site resulted in an improvement in performance in a visual search task in certain conditions. The task involved searching for a target composed of a conjunction of features also present in a set of distracters (e.g., the target might be a red letter “T” among a set of red “L”s and green “T”s). When one of the features of the search was direction of motion, TMS given over the occipital site, identified as motion analysis area V5, delayed RT. On the other hand, TMS applied to the same site decreased RT when the conjunction target was based only on form and color and not motion. This suggests a competition among the various visual cortical areas which process different properties of incoming stimuli in parallel. In the case where information about the movement of the stimuli was irrelevant, disruption of competing but irrelevant movement information from a motion processing region may have decreased the total processing time necessary to evaluate stimulus information and make a decision. Most likely for very similar reasons, in a different study single TMS pulses to V5 increased RT in a motion discrimination task, but enhanced RT when the task was object discrimination, where the critical visual processing is in more ventral posterior cortex (Alford et al., 2007).

One Hz rTMS is thought to lower local cortical excitability, and trains of 1Hz rTMS of sufficient duration (10-20 minutes) have been described as producing temporary “lesions” in targeted cortex (Pascual-Leone et al., 1999). This makes the use of 1Hz stimulation an interesting candidate to produce performance enhancements via the addition-by-subtraction mechanism, and there are indeed a number of examples where this may have taken place. Once again using the example of visual search, in one variant form the distracters used can be modulated in their salience (i.e., in their ability to capture attention), for instance by making a distracter a bright color compared to the other distracters and the target in the search array. The presence of such a strong distracter slows RT. However, 10 min of 1Hz rTMS applied to right posterior parietal cortex, an area involved with directing attention to salient stimuli, removed this RT cost, enhancing RT in this situation (Hodsoll et al., 2009). Another use of 1Hz down-modulation is to produce behavioral enhancements through release from cross-hemispheric inhibition (Hilgetag et al., 2001; Thut et al., 2005, Kobayashi et al., 2010). Besides 1 Hz rTMS, continuous theta burst stimulation is also thought to down-regulate cortical excitability, and was used on visual area V5 in a visual search task to enhance target detectability by the same group that used single pulses to V5 to enhance visual search performance, providing further evidence for their suggested addition-by-subtraction mechanism (Kalla et al., 2009).

Enhancement effects due to higher frequencies of rTMS may also be explained by an addition-by-subtraction mechanism. For example, short trains of 12Hz stimulation to right parietal area improved accuracy of object identification, a performance facilitation the authors suggested may have resulted from disinhibition of ventral occipital object identification areas (Harris et al., 2008). Another example was reported by Hayward et al. (2004), in which short trains of 10Hz rTMS to anterior cingulate cortex led to the abolition of RT costs to incongruent stimuli in a Stroop task. This may have occurred through the disruption of conflict resolution processing in a situation where it was unnecessary, only slowing down performance.

In summary, the addition-by-subtraction mechanism underlying performance enhancement by TMS appears to function by disrupting or inhibiting an inessential or less essential but competing part of one or more functional brain networks involved in a task resulting in temporary network reorganization. This reorganization can occur on a dorsal/ventral (e.g, Alford et al., 2007; Harris et al., 2008), left/right (e.g., Hilgetag et al., 2001), and/or anterior/posterior (e.g., Snyder et al., 2006) axes. Addition-by-subtraction can occur by either disrupting ongoing processing with single pulse TMS or higher frequency rTMS, or by down-regulation in cortical excitability caused by longer trains of 1Hz rTMS. The studies in which TMS-caused enhancements appear to be related to this mechanism are listed in Table 2.

Potential uses of TMS-induced performance enhancement

Potential applications of TMS cognitive enhancement include research into cortical function, treatment of neurological and psychiatric illness, and skill acquisition in healthy individuals. Manipulation of enhancement effects adds to the experimental palette of brain stimulation techniques examining cortical processing. For example, 1Hz rTMS inhibition of V5 led to understanding of a spatial suppression effect in visual motion perception (Tadin et al., 2011). Right parietal stimulation inhibited suboptimal processing in visual search, shedding light on the cortical dynamics of learned strategy changes (Oliveri et al., 2010). Stimulation of motor cortex before practicing a skilled thumb movement provided evidence for a theory concerning the contribution of interhemispheric interactions facilitating motor control (Kobayashi et al., 2010). Instead of passively observing brain states with brain imaging and EEG alone, TMS provides the ability to directly intervene with ongoing processing to causally test hypotheses, and being able to enhance performance with TMS allows modulation in two directions, enabling clear double dissociations even in the same cortical region. For example, bursts of rTMS in theta and beta frequency ranges to parietal cortex produce opposite effects in processing local and global features of the same stimuli, demonstrating different functional roles in cortical oscillatory behavior (Romei et al., 2010.

TMS performance enhancement can be used to directly facilitate neuroplastic and therapeutic effects in recovery from stroke (Bashir et al., 2010), in TBI (Cicerone et al., 2006), and in Alzheimer's disease (Nardone et al., 2012). TMS has repeatedly demonstrated facilitatory effects in neurorehabilitation after stroke (Bashir et al., 2010; Khedr et al., 2005; Mansur et al., 2005; Takeuchi et al., 2005; Fregni et al., 2006; Wang et al., 2012). For example, investigators applied trains of 10Hz rTMS to patients with hemiparesis who alternately completed practice trials of a sequential finger motor task (Kim et al., 2006). Over the course of a session patients showed significantly improved movement accuracy and speed. In line with suggested enhancement mechanisms based on a Hebbian TMS/task performance confluence , a recent study that used 5Hz rTMS in conjunction with physical therapy across ten sessions resulted in better clinical improvement above physical therapy alone that were sustained over a 12 week period (Emara et al., 2010). Such studies provide strong evidence for the potential clinical usefulness of TMS in post-stroke recovery. Similar use of TMS has also been suggested in accelerating therapies in TBI (Cicerone et al., 2006). TMS may also directly act to improve memory and language function in elderly patients, sometimes for periods of at least eight weeks (Sole-Padulles et al. 2006; Cotelli et al., 2006; 2008; 2011). For example, Sole-Padulles et al. (2006) found that 5Hz rTMS applied to the prefrontal cortex significantly enhanced performance on a face-name memory task in 40 subjects with impaired memory. Subjects showed increased activity in the occipital and prefrontal regions, suggesting that rTMS aided the recruitment of a compensatory neural network that led to enhanced performance, and that rTMS may thus be of use in staving off cognitive decline in dementia.

Improvements in performance caused by TMS may also prove to be beneficial to otherwise healthy individuals. Application of brain stimulation techniques to aid human operators in performance of work was proposed in a recent review (McKinley et al, 2012) as an extension of “neuroergonomics,” a new field of research discussed by Parasuraman and

Rizzo (2008). They suggested that brain stimulation-produced enhancements might serve to deal with the growing misalignment of human abilities with the increasing capabilities of modern technology. One means of using TMS (in this case, through addition-by-subtraction) to improve skills has been popularized by Snyder and colleagues (Snyder et al., 2006; 2009). Snyder et al. note that some brain-impaired individuals (savants) are capable of amazing feats of cognition in very restricted areas, that these skills are literal and non-symbolic, and that they may derive from more direct access to raw sensory experience. They suggest 1Hz rTMS applied to anterior temporal and prefrontal cortical regions may inhibit conceptual and symbolic thought, allowing this direct access to raw perception and evoking “savant-like” ability in otherwise normal individuals, and have reported some success in using TMS in this manner (e.g., in enhancing numerosity skill: Snyder et al., 2006). While our knowledge of which cortical areas may be most efficiently inhibited to produce savant-like skill may still need development, the concept itself appears promising. A simple example was reported by Oliveri et al. (2010), where targets and distracters in a visual search task were identical except that the target was rotated relative to the distracters. The stimuli were shaped like the letter “X,” but if identified as such by higher conceptual centers, targets and distracters were much harder to distinguish (when identified as “X's” they tend to be seen in the canonical upright form, blurring the distinction between target and distracter), whereas if the simple feature of orientation was used alone, as could be done in visual areas lower in the processing hierarchy (i.e., where “raw” perception occurs), the task was more easily accomplished. True to this conception, when 1Hz rTMS was used to inhibit conceptual activity in parietal cortex, subjects performed better. As knowledge of functional cortical networks grows, TMS may be targeted more efficiently to enhance cognitive skills, and, with development of TMS-assisted Hebbian-like learning, to possibly accelerate the learning process.

Refinement of TMS enhancement induction techniques

The potential applications of TMS cognitive enhancement are exciting, but they presently remain at the stage of promise. This is because the reported enhancement effects are in general weak in size and short-lived, lasting from a few seconds in the case of short stimulation trains to ten minutes to an hour with offline stimulation. However, TMS is still a relatively new technology, and there is much that can be done to optimize its use. TMS targeting can still be improved and more fully integrated into brain imaging. The parameter space for stimulus delivery is quite large (including frequency, train duration, intensity, number of trains, stimulus waveform and polarity) and has been little explored, and the knowledge of the interaction of TMS with neural systems that could be used to intelligently explore that space is still only rudimentary (Hoogendam et al., 2011).

The spatial resolution of TMS is not likely to improve dramatically given current coil design and materials generally available, but what can be improved in terms of spatial parameters is to make the targeting of the peak magnetic field as efficacious as possible. Great progress along these lines has been made: targeting technology has rapidly matured over the last decade, advancing from marking scalp sites using the International 10-20 System used in EEG, which can only target with a resolution of a few centimeters due to the variable nature of head and brain anatomy (Homan et al., 1988), to positioning according to individual fMRI brain activation. An advance occurred when frameless stereotaxic systems were developed for the co-registration of the TMS coil to individual structural high resolution MRI scans and permitted the targeting of individual sites of activation found by fMRI. The differences between TMS targeting strategies have been illustrated in a study by Sack et al. (2009), in which it was found that only five subjects were needed to observe a behavioral effect of TMS on a task when individual fMRIs were used for targeting, while double that number were required to see the same effect when structural MRIs or group-analyzed fMRI were used, and 47 subjects were needed when the 10/20 EEG system was used. Development of robotic coil positioning systems that will remove human error in positioning and repositioning coils, as well as subject movement (Mattheus et al., 2008) will lead to targeting the precise, individualized targets provided by imaging with millimeter resolution. Targeting can be further improved by using realistic head modeling to guide placement of the coil to individual brain anatomy, as well as modeling the interaction of electric fields with gyral anatomy (Silva et al., 2008). For example, the efficacy of TMS in stimulating motor cortex, as measured by MEPs in targeted muscles, is extremely sensitive to coil orientation (Balslev et al., 2007), and this is thought to be due to the direction of the current induced by the coil relative to the orientation of the stimulated cortical gyrus (Thielscher, 2011). Also, the development of concurrent fMRI/TMS has made clear that brain stimulation has effects beyond the targeted region (Reithler et al., 2011). These effects need to be taken into account in interpreting TMS enhancement. However, such interpretations are not always straightforward. For example, offline theta burst TMS applied to left motor cortex resulted in speedier right hand responses in a choice RT task, as well as increased fMRI activation of the left motor cortex (Cardenas-Morales et al., 2011). This follows the previously stated keys for TMS enhancement from direct stimulation- that high frequency be used immediately before testing. However, similar speeded response was also seen with the left (ipsilateral) hand, which is not so easily explained and suggests some sort of premotor or prefrontal involvement in the enhancement. One exciting development in using MRI to aid targeting involves using MRI tractography: TMS to a medial frontal gyrus location connected (as demonstrated with DTI) to a TMS hot spot for thumb sensation in somatosensory cortex enhanced RT in a tactile working memory task, while TMS to a nearby but unconnected site in the same gyrus did not (Hannula et al., 2010). Further integration of TMS with brain imaging in modeling the cortical target and in tracing the distributed effects of stimulation will continue to improve TMS targeting and thus, enhancement effects. TMS has special potential in this regard because it can be integrated into imaging in ways other types of noninvasive brain stimulation like tDCS cannot, as its high temporal resolution allows it to be interleaved with MRI for the generation of concurrent TMS/fMRI.

Beyond spatial targeting, the effects of other TMS parameters are only crudely understood, and greater exploration of the large parameter space involved with TMS could lead to improvements in enhancement techniques. For example. the exact shape and duration of a TMS waveform plays a key role in the degree of neural response (Peterchev et al., 2011; Kammer et al., 2001), and the optimal waveforms needed to stimulate the membranes of target neurons remain to be investigated. Also, the finding that at low stimulus intensity TMS to V5 facilitated motion discrimination performance while at high intensities it disrupted performance (Schwarzkopf et al. 2011) indicates that TMS intensity level can play a crucial role in determining whether enhancements occur.

There is also a great need for sophisticated modeling of the dynamic responses of large systems of neurons to brain stimulation. It has become increasingly clear that the prior state of a cortical region and its associated network connections strongly influences the effect of TMS (Silvanto et al., 2008a). Prior brain stimulation can change whether cortex is up or down regulated in excitability by a train of rTMS (Silvanto et al., 2008b) and whether enhancement or disruption effects are found (Siebner, 2004). Prior stimulation of a distant region such as cerebellum can abolish LTP-like effects in motor cortex (Hamada et al., 2012). Prior state of indigenous neural oscillations has been shown to effect response to TMS (Romei et al., 2008). Prior neural processing in the stimulated region also can affect response to TMS. In the enhancement literature reviewed here for example, visual adaptation to a letter stimulus determined what new stimuli would be responded to with enhanced or impaired performance (Cattaneo et al., 2008; 2009b). Prior knowledge of which of two visual search tasks is to be performed (and thus of prior modulation of attentional set via top-down processing) is necessary for facilitation of RT (Ellison et al., 2005). In all these ways the state of the cortical region being stimulated plays a large role in determining whether disruption or enhancements occur, and any ability to predict enhancements must rely on cortical modeling.

A promising start in dynamic modeling occurred with a simulation of the response of 30,000 motor cortex neurons within a thalamocortical system, including over five million intra- and inter-cortical layer synaptic connections, to single and paired TMS pulses (Esser et al., 2005). The output of the model system was able to reproduce the effects seen in electrophysiological response to TMS pulses in epidural electrodes of varying stimulation frequency, timing, and dose, as well as with pharmacological manipulations,. Much, however, remains to be done. For example, receptive field properties of neurons and their changes with prior and ongoing processing should be included in neural modeling. One very interesting approach to explaining some effects of TMS on performance suggests that TMS disrupts ongoing processing in a cortical region by reducing signal-to-noise ratio (Ruzzoli et al., 2010, 2011; Silvanto and Muggleton, 2008); that the relationship of signal level and TMS intensity can lead to facilitating phenomena such as stochastic resonance (Miniussi et al., 2010; Schwarzfopf et al., 2011); and that the TMS pulse more strongly affects neurons that are less active at the moments of stimulation (e.g., Ruzzoli et al., 2010). On this latter point, it is useful to note that while a TMS pulse immediately prior to the detection of a stimulus may temporarily raise the level of excitation in all neurons in a region and possibly produce enhancement of detection accuracy through a mechanism such as stochastic resonance (as may have happened in, for example, Grosbras and Paus, 2002; 2003), this would not be the case if the task was to make a discrimination using the properties of opposing receptor field types, as all neurons receive more or less the same amount of excitatory boost. However, one way to take advantage of the possibility that it is the less active neurons that respond most strongly to TMS is to change the activity level of neurons in a cortical area differentially according to their receptor field properties through techniques such as adaptation and priming (Silvanto et al., 2008a). Specific facilitations using these techniques in discrimination paradigms have been successfully induced for attributes such as numerical magnitude (Cohen-Kadosh et al, 2010; Renzi et al, 2011), actions (Cattaneo et al, 2010), and semantic categories (Cattaneo et al, 2011)

Another aspect of neural modeling that demands attention concerns the functionality of neural oscillations in controlling or modulating local processing in cortical circuitry and in coordinating distant regions, as well as the local and distributed oscillatory response to single TMS pulses and to trains of various frequencies of rTMS. The capacity of rTMS to reset (Van Der Werf and Paus, 2006), drive and modulate cortical oscillations (Thut et al., 2011) needs to be better understood, especially given the frequency specificity of TMS enhancement effects (Klimesch et al., 2003; Luber et al., 2007a; Romei et al., 2010), and the apparent greater efficacy of theta burst stimulation, with its more complex nesting of gamma and theta frequencies. In the latter case for example, just a little over three minutes of excitatory theta burst stimulation to motor cortex sped subsequent RT for 40 minutes after the end of stimulation (Cardenas-Morales et al., 2011), and twenty seconds of inhibitory theta burst produced accuracy increases for thirty minutes in a visual search task (Kalla et al., 2009). Overall, a great deal still needs to be learned about the interaction of TMS and cortex. It is not unreasonable to assume that as more is learned and better modeled, enhancement of performance by TMS can be better predicted and effects considerably amplified.

Another serious issue is the short duration of TMS performance enhancements. Enhancement effects of single pulse and brief rTMS trains do not appear to last more than a few seconds acutely. For example, 5Hz rTMS trains to parietal cortex facilitated RT when applied during the retention period between encoding and retrieval in a WM task, but no facilitation occurred in the non-TMS trials which alternated with ones in which rTMS was applied (Luber et al., 2007a). When explicitly tested, no spill-over or cumulative effects of 3 s trains of 10Hz rTMS were found in a visual recognition task (Hamidi et al., 2011). Plasticity effects due to long or multiple trains of rTMS generally last a few minutes to an hour. When measured, those producing cognitive enhancement reported similar durations in performance changes, from two minutes (Sparing et al., 1999; Mottaghy et al., 1999) to ten minutes (Kobayashi et al., 2010; Thut et al., 2005) to one or two hours (Butefisch et al., 2004, Tegenthoff et al., 2005), although using theta burst stimulation, Galea et al. (2010) reported effects lasting six hours.

The reasons for limited durations of TMS effects are not known, but some mechanisms are beginning to be understood. Cortical neural systems tend to be homeostatic (Jung et al., 2008), resisting changes caused by external disruptions such as TMS, generating reactions such as local habituation or adaptation (Chen et al., 1997) or systemic learning within the TMS context through conditioning (Luber et al., 2007b) or practice (Gagnon et al., 2011). Nonetheless, two manipulations may have the potential to increase the duration of TMS performance enhancement substantially. First, it has been reported that increasing the duration of 5Hz rTMS to motor cortex increases the subsequent duration of MEP modulation (Peinemann et al., 2004). Given that repeated sessions of rTMS have already been shown to cause long-lasting changes in mood (e.g., O'Reardon et al., 2007) and in recovery of motor function from stroke (Emara et al., 2010), it has been suggested that repeated sessions of rTMS may also prolong the duration of cognitive benefits as well (Thut and Pascual-Leone, 2009). The second manipulation, suggested by Ragert et al. (2003) and Thickbroom (2007), is that beneficial TMS effects might be prolonged through Hebbian-like learning, by co-activation of a targeted cortical region by rTMS and task performance. According to Thickbroom (2007), an rTMS session can be conceived as a four part procedure: an immediate pre-rTMS period, an application period, an immediate post-application period during which plasticity mechanisms are up-regulated, and a later post-application period when neural excitability has returned to baseline. Having a subject practice a given task associated with a target cortical region prior to stimulation might prime the target network. Performing the task during rTMS application in a time-locked fashion might result in confluent Hebbian activation, potentiating the synapses central to processing the task. Task performance immediately after rTMS application, while the targeted cortical region remains modulated by the stimulation, could continue this neural network training.

The possibility of prolonging TMS-induced cognitive enhancement was tested in a series of experiments based on the enhancement of WM with 5Hz rTMS we found in Luber et al. (2007a). We created a deficit in WM performance using sleep deprivation: sleep deprived individuals will typically exhibit response slowing and lapsing (missed responses) during the task (Lim and Dinges, 2008). We used fMRI-guided rTMS to find an appropriate cortical network (Habeck et al., 2004), test its amenability to enhancement with rTMS (Luber et al., 2008), and finally tested whether concurrent rTMS/task performance over multiple sessions would prolong the rTMS-caused enhancement (Luber et al., 2013).

Initially, fMRI was used to identify a cortical network activated by a WM task that was also sensitive to sleep deprivation, in the sense that network activation decreased as WM performance decreased pre- and post-sleep deprivation (Habeck et al., 2004). fMRI-guided rTMS was then used to remediate performance in sleep deprived individuals (Luber et al., 2008). In subjects who had experienced total sleep deprivation for two days, 5Hz rTMS was applied during the retention phase of the WM task. The fMRI network associated with sleep deprivation-induced performance impairments in this task was used for targeting. rTMS to a left lateral occipital site within the network resulted in a reduction of the sleep-induced RT deficit without a corresponding decrease in accuracy, while stimulation outside the network did not. In pre-post sleep deprivation fMRI scans, the degree of performance enhancement with rTMS correlated with the degree to which each individual failed to sustain activation of the fMRI network. These results demonstrated that rTMS had modulated a cortical network critical to the WM task in a way that improved its resilience to sleep deprivation.

We then implemented two potential manipulations to prolong beneficial cognitive rTMS effects by co-activating targeted cortex with rTMS while subjects performed the WM task, and did so repeatedly in four sessions over the course of two days of sleep deprivation (Luber et al., 2013). In testing WM performance at the end of the sleep deprivation period, eighteen hours after the last TMS session, sleep deprived subjects receiving active 5Hz rTMS performed the WM task similarly to non-sleep deprived individuals, while sleep deprived subjects receiving sham rTMS showed all the slowing and lapses typical of sleep deprived individuals. These results suggest that rTMS applied in multiple sessions coupled with co-activation with WM task performance affected neural circuitry involved in WM to prevent the full impact of sleep deprivation on processing involved with the task from occurring. Most important in the present context, a beneficial cognitive effect of rTMS was demonstrated a full eighteen hours after the last of four sessions of concurrent rTMS/task performance, demonstrating a prolongation of benefit an order of magnitude longer than is typically reported in studies of TMS performance enhancement. This result suggests that long lasting TMS cognitive enhancement and a technology of specific skill enhancement using brain stimulation may be possible.

Conclusion

Over sixty reports of TMS performance enhancement have accumulated over the last decade and a half, and many more are likely as the technology of TMS is refined, and as knowledge of cortical network dynamics builds. Increasing our understanding of enhancement mechanisms such as addition-by-subtraction, potentiating oscillatory behavior, and promotion of Hebbian-type learning may result in acute facilitation of skills needed to interact with ever more complex information technology as well as long-lasting therapeutic benefits for those with neurological and psychiatric illnesses and accelerated learning of useful skills in healthy individuals. TMS itself can be expensive, especially when used in conjunction with brain imaging, and may ultimately be supplanted for common use by cheaper alternatives such as transcranial direct current stimulation (tDCS), but, given its superior spatial and temporal resolution, its present impact on researching cognitive enhancement is clear.

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Highlights

1. We have found 61 reports in which TMS enhanced cognitive performance, rather than disrupting it
2. Mechanisms of TMS enhancement include nonspecific, direct and indirect classifications
3. Applications of TMS enhancement include research, therapy, and skill acquisition
4. A great deal can still be done to strengthen TMS enhancement effects
5. In particular, new methods may result in long lasting TMS cognitive enhancement

Table 1

Studies reporting performance enhancements with TMS targeting regions expected to be directly involved in a given task.

TMS Dosage	**On-Line / Off-Line**	**reference**	**task**	**performance effect**
Single pulse	*on-line*	Butefisch et al., 2004	motor learning	increased accuracy
		Cattaneo et al., 2010	action discrimination	decreased RT
		Cattaneo et al., 2008; 2009b	letter discrimination	decreased RT
		Cattaneo et al., 2009a	nonverbal working memory	decreased RT
		Grosbras & Paus 2002; 2003	backward masking	increased detection sensitivity
		Hannula et al., 2010	tactile working memory	decresed RT
		Renzi et al., 2011	numerical magnitude judgment	decresed RT
		Stoeckel et al., 2009	homophone & synonym judgment	decreased RT
		Topper et al., 1998	picture naming	decreased RT
		Van Ettinger-Veenstra et al.,2009	visual discrimination	increased accuracy
Paired pulse	*on-line*	Gagnon et al., 2011	verbal & non-verbal recognition	decreased RT
		Sakai et al., 2002	syntactic decisions about sentences	decreased RT
		Wipfli et al., 2001	memory-guided eye movement	decreased RT
High Frequency	*on-line*	Boroojerdi et al., 2001	visual analogic reasoning	decreased RT
		Cappa et al., 2002	picture naming	decreased RT
		Cohen-Kadosh et al., 2010	numeral discrimination	decreased RT
		Cooper et al. 2004	visual attention	increased accuracy
		Evers et al., 2001	visual go-nogo	decreased RT
		Klimesch et al., 2003	mental rotation	increased accuracy
		Kohler et al., 2006	word recognition	increased accuracy
		Luber et al., 2007	letter working memory	decreased RT
		Mottaghy et al., 1999	picture naming	decreased RT
		Romei et al., 2011	visual discrimination	decreased RT
		Schwarzkopf et al. 2011	motion discrimination	increased accuracy
		Sparing et al. 2001	picture naming	decreased RT
		Yamanaka et al., 2010	spatial working memory	decreased RT
Low Frequency	*off-line*	Waterston and Pack, 2010	visual discrimination	increased accuracy
High Frequency	*off-line*	Boyd et al., 2009	motor tracking	decreased movement error
		Hwang et al., 2010	continuous performance	increased accuracy

TMS Dosage	On-Line / Off-Line	reference	task	performance effect
		Ragert et al., 2003	tactile discrimination	lowered sensory threshold
		Tegenthoff et al., 2005 Cardenas-Morales, 2011	tactile discrimination motor choice RT	lowered sensory threshold decreased RT

Table 2

The studies in which TMS-caused enhancements appear to be related to the addition-by-subtraction mechanism

TMS Dosage	On-Line / Off-Line	reference	task	performance effect
Single pulse	*on-line*	Alford et al., 2007	object categorization	decreased RT
		Ellison et al. 2003	visual search	decreased RT
		Walsh et al., 1998	visual search	decreased RT
		Koski et al., 2004	visual detection	decreased RT
		Lou et al., 2010	adjective judgment	decreased RT
		Muri et al., 1999	directed eye movement	decreased RT
		Seyal et al., 1995	somatosensory detection threshold	decreased detection threshold
Low Frequency	*on-line*	Kirschen et al., 2006	verbal working memory	decreased RT & higher accuracy
	off-line	Drager et al., 2004	picture-word match	decreased RT
		Galea et al., 2010	visuo-motor sequence learning	decreased RT
		Kobayashi et al., 2010; 2004; 2009	visuo-motor sequence learning	decreased execution time
		Hilgetag et al., 2001	spatial attention	increased detection accuracy
		Thut et al., 2005	spatial attention	increased detection accuracy and decreased RT
		Hodsoll et al., 2009	visual search	decreased RT
		Oliveri et al., 2010	visual search	decreased RT
		Knecht et al., 2002	picture-word verification	decreased RT
		Schutter & van Honk, 2006	sequential item memory	increased accuracy
		Snyder et al., 2006	numerosity	increased accuracy
		Tadin et al., 2011	motion discrimination	decreated detection threshold
High Frequency	*on-line*	Sauseng et al., 2009	working memory	increased capacity
	off-line	Harris et al., 2008	object identification	i ncreased accuracy
		Hayward et al. 2004	Stroop	decreased RT
		Rushworth et al., 2001	spatial attention	decreased RT
Continuous Theta Burst	off-line	Kalla et al., 2009	visual search	increased detection accuracy