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NEUROMODULATION (S TAYLOR, SECTION EDITOR)

Enhancing Cognition with Theta Burst Stimulation

Elise Demeter[1]

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Abstract Theta burst stimulation (TBS) protocols are believed to produce more reliable, longer-lasting effects on cortical dynamics and on behavior than other standard forms of transcranial magnetic stimulation (TMS). Most TBS experiments use stimulation to a targeted region to impair cognitive function, allowing for causal inferences between anatomical locations and cognitive processes to be drawn. However, this review covers a small but rapidly growing literature suggesting TBS can also benefit cognitive performance. These pro-cognitive effects have been observed in both healthy individuals and in clinical populations. While these data are promising, the available evidence also suggests the effects of TBS may be dose, state, and site specific. Overall, this line of research is of high interest for understanding how the brain mediates cognitive functions, investigating the potential plasticity of these neural mechanisms, and for developing treatments for the cognitive impairments found in many neuropsychiatric and neurological disorders.

Keywords Theta burst stimulation · Transcranial magnetic stimulation · TMS · Cognitive performance · Enhancement · Memory · Attention · Spatial neglect · Depression

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✉ Elise Demeter
emd7@duke.edu

[1] Center for Cognitive Neuroscience, Duke University, B242B LSRC Building, Box 90999, Durham, NC 27708-0999, USA

Introduction

Transcranial magnetic stimulation (TMS) has become a core method for studying the role of cortical brain regions in cognitive functions. TMS works by applying brief, high-intensity magnetic fields to the scalp, which induces currents in the underlying cortical tissue and thus depolarizes neurons in the targeted brain region. Most studies using TMS to study brain function create so-called virtual lesions, temporarily perturbing neuronal firing in a targeted cortical region and studying the resulting impairments in cognitive function [1]. This method is extremely useful for making causal inferences about the role of cortical regions in cognitive processes. However, a small but growing literature also indicates that TMS can facilitate cognition. This work has exciting implications both for studying cognitive functioning in healthy populations and for treating cognitive impairments in special populations. Here, I review the literature using a specialized form of TMS, theta burst stimulation (TBS), to improve cognition.

Enhancing Cognition with TMS

Many early findings that TMS could enhance cognition were attributed to "paradoxical" facilitation, where TMS disrupted distracting or competing stimulus elements, allowing more efficient processing of task-relevant stimuli (e.g., [2]). However, over 70 studies to date have found TMS-associated cognitive improvements, using a variety of TMS protocols and cognitive tasks (see [3] for a recent review). While some results may stem from disrupting competing processes, some pro-cognitive effects may result from TMS facilitating task-relevant processing in the targeted region or in connected neural networks. For example, high-frequency repetitive TMS (rTMS; typically 5 or 20 Hz) is thought to facilitate cortical processing

and has been shown to improve visual perception [4], mental imagery [5], working memory [6], and episodic memory [7, 8].

While these pro-cognitive effects are exciting, enthusiasm for the use of TMS to enhance cognition has been dampened by substantial variability in physiological and behavioral responses to TMS across and within participants and weak, short-lasting effects on behavior [9–11]. For instance, short trains of TMS may improve behavioral performance for only a few seconds, while longer stimulation times (~10–25 min) of administered offline may produce improvements that last 10 min to an hour post-stimulation. The development of alternative stimulation protocols that might produce more reliable and persistent effects has thus generated substantial interest.

Theta Burst Stimulation Protocols

Introduced in 2005 [12], theta burst stimulation (TBS) was designed after "theta burst" paradigms used to induce long-term potentiation or depression in animals [13–16]. Compared to other forms of TMS, TBS is designed to more closely mimic the brain's natural firing patterns and may have more robust effects on cognitive performance. TBS is thought to affect neural plasticity through GABAergic and glutamatergic mechanisms [17, 18]. In humans, TBS delivers very short, high-frequency stimulation pulses to the scalp at intervals, typically three stimulation pulses delivered at 50 Hz (gamma frequency) and repeated every 200 ms (theta frequency intervals of 5 Hz). The combination of gamma frequency stimulation applied at theta rhythm is thought to mimic theta-gamma coupling hypothesized to play a role in cognitive functions such as working memory [19]. In continuous TBS (cTBS) protocols, TBS is delivered in an uninterrupted train for roughly 40 s. In intermittent TBS (iTBS), 2-s trains of TBS are repeated every 10 s, for approximately 190 s in total.

TBS's Effects on Brain Activity

An advantage of TBS is its ability to induce long-lasting effects on cortical excitability with relatively short stimulation times. Much of what is known about TBS's effects on cortical dynamics is from the primary motor cortex (M1), where motor evoked potentials (MEPs) can be used to directly measure stimulation's effect on motor function. A quantitative review of TBS studies in M1 found 40 s of cTBS significantly suppressed cortical excitability for up to 50 min, while 190 s of iTBS significantly facilitated cortical excitability for up to an hour [20••]. These data suggest TBS could also be very useful for inducing reliable, long-lasting effects on behavior.

A degree of caution is warranted, however, as several parameters can influence TBS's effects on cortical excitability. cTBS is generally considered inhibitory and iTBS facilitatory, but reversals of these patterns have been observed [21] and the after-effects of TBS may be dose dependent [21, 22••]. Participant demographics (including age) or health factors can influence responses to TMS, as can brain state at the time of stimulation (i.e., at rest or engaged in a cognitive task [9, 23]).

Furthermore, some evidence suggests effects seen in the motor cortex may not always translate to other cortical regions [24–26]. Studies that combine TBS with other methods for measuring brain activity, such as functional magnetic resonance imaging (fMRI) or electroencephalography (EEG), are thus of particular value. Such work has shown TMS, including TBS, can induce changes in brain activity both in the targeted region and in functionally or structurally connected regions [27, 28••, 29••, 30, 31, 32•]. Stimulating specific subregions can lead to site-specific activation changes in distinct cortical-subcortical networks [28••, 33]. For example, one study found stimulating the lateral prefrontal cortex (PFC) produced differential activation in the hippocampus while medial PFC stimulation differentially activated the caudate [33].

TBS as a Cognition Enhancer

TBS may be a powerful technique for modulating brain functioning and enhancing cognitive performance. However, given the number of variables in the TBS parameter space, a priori predictions of how TBS may affect cognition are not always straightforward. Approximately two dozen publications to date have successfully used TBS to enhance cognition, with many reports occurring within the last 2 years. This review is organized by area of cognitive function and focuses primarily on studies using healthy participants. A section at the end discusses investigations using TBS to enhance cognition in clinical populations.

Enhancing Motor and Somatosensory Functions

It is relatively easy to evaluate the impact of TBS on cortical excitability in M1 and in primary somatosensory cortex (S1) by measuring MEPs and somatosensory evoked potentials (SEPs), respectively. The available data indicate cortical excitability in both regions is suppressed with cTBS and facilitated with iTBS [20••, 23, 34–36]. Targeting M1 with iTBS can improve motor learning in healthy individuals [37, 38], by increasing M1 excitability (and presumed synaptic plasticity) and by increasing performance variability within participants in a manner that correlated with learning outcomes [38]. Applying iTBS to S1 has been shown to improve behavioral performance on tactile perception tasks and somatosensory temporal discrimination tasks [39, 40]. These pro-cognitive effects in healthy populations are promising and are of particular relevance to those interested in using TBS to treat motor disorders. However, outside of M1 and S1, the available

literature on the pro-cognitive effects of TBS is substantially more complex.

Enhancing Memory Function

Several recent studies report TBS to frontal sites can improve memory performance. Some findings can easily be attributed to "paradoxical" facilitation, where disruption of a competing cognitive process leads to the enhancement of another (e.g., [41, 42]). However, there are also effects most easily interpreted as direct TBS-induced enhancement of the neurophysiological processes mediating specific memory functions [29••, 43••, 44].

Working Memory

In the domain of working memory, a 2015 investigation found iTBS to the left dorsolateral prefrontal cortex (dlPFC) significantly improved working memory performance in healthy subjects [29••], consistent with earlier findings of working memory impairment following cTBS [31]. In this two-session, repeated-measures design study, active or sham iTBS was delivered to the left dlPFC. Participants' working memory was assessed using a classic *n*-back task with letter stimuli (2-back and 3-back memory loads) at 0, 20, and 40 min post-stimulation. Compared to sham, active iTBS produced a robust improvement in 2-back accuracy at 20 and 40 min post-stimulation (*d*' scores increased by ~0.6 with active iTBS). However, no improvements were seen in the 3-back condition, suggesting there are limits to how much iTBS can improve cognitive performance in healthy individuals.

A particularly interesting facet of this study was that electroencephalography (EEG) was recorded during working memory performance. The improved 2-back performance following active iTBS was accompanied by increases in theta connectivity between left dlPFC and bilateral parietal channels and an increase in parietal gamma power. Increased gamma was also observed in the 3-back. Theta and gamma frequencies are both implicated in the working memory, with theta thought to integrate information across the working memory frontoparietal network and gamma implicated in local sensory processing [19]. TMS can entrain oscillations at the stimulation frequency [45]. Thus, left dlPFC iTBS could have altered specific neurophysiological processes underlying the working memory, leading to enhanced 2-back accuracy.

Episodic Memory

TBS can also improve long-term episodic memory performance. In Blumenfeld et al., the role of prefrontal subregions in long-term memory encoding was investigated using cTBS [46]. Left ventrolateral PFC or dlPFC was stimulated before participants performed a semantic encoding task and subsequent recognition memory test. While ventrolateral PFC stimulation led to memory impairments, there was a trend for enhanced recognition following dlPFC stimulation. My colleagues and I also found evidence that iTBS to dlPFC just prior to encoding can improve subsequent long-term memory [44]. In a pair of experiments, we applied short, 2-s bursts of TBS to the left dlPFC immediately prior to the encoding of semantic stimuli. We found enhanced subsequent recognition memory for items encoded following dlPFC stimulation compared to memory for items encoded after vertex stimulation.

In both of these investigations, participants were asked to encode semantic items using a deep encoding strategy (e.g., make abstract or concrete judgments about items), a level of processing manipulation designed to promote successful retrieval of studied items [47]. Previous research demonstrates deep encoding strategies engage left frontal regions to a greater extent than shallow strategies [48–50]. A recent iTBS-fMRI study provides insight into how TBS affects the brain networks involved in encoding [51•]. In this study, healthy older adults were scanned before and after receiving active or sham iTBS to the left frontal cortex. In the scanner, participants performed a semantic encoding task involving blocks of deep and blocks of shallow encoding strategies. Out of the scanner, participants were tested on their recognition memory for studied and novel items. Notably, the investigators found no evidence that active iTBS improved the older adults' memory performance. However, they did find that active iTBS increased left frontal activation and activation in occipital cortex and cerebellum, as well as the functional connectivity between left frontal and occipital-cerebellar regions. Importantly, these findings were specific to the deep encoding condition and were not observed during shallow encoding. This suggests the improvements in subsequent memory performance previously observed [44, 46] were a result of modulating brain network activity specific to deep encoding processes.

Memory Awareness and Prospective Memory

Recent studies have examined TBS's effects on other aspects of memory functioning, namely memory awareness and prospective memory. Memory awareness, or the monitoring of memory performance, is critical for optimizing learning and memory [52]. In a three-session, within-subjects design study [53••], cTBS was administered to dlPFC, to frontopolar cortex, or to a control location over the central fissure. Participants then studied fractal and object pairs and were later tested on their memory for associated pairs. During the study, participants made judgments of learning (JOLs) to indicate the likelihood they would later remember an associated pair. The authors found cTBS selectively to the frontopolar cortex significantly improved participants' accuracy at correctly

predicting their future associative memory. Frontopolar stimulation also led to higher confidence scores for correct trials during the memory test. This enhanced memory awareness was unexpected, as inhibitory cTBS might have been predicted to impair memory awareness.

Frontopolar cortex is also implicated in prospective memory, or the ability to delay the execution of a previously formed intention. This region's role in prospective memory function was probed using both iTBS and cTBS in a group of healthy older adults. iTBS to left frontopolar cortex significantly improved performance in a virtual reality-based prospective memory task compared to stimulation of the vertex [43••]. cTBS to the frontopolar cortex produced no effects on behavior.

Collectively, the available data on TBS's pro-cognitive effects in memory tasks underscore the difficulty of predicting frontal TBS's effects on behavior. They also demonstrate the usefulness of including both iTBS and cTBS conditions in experiments looking for pro-cognitive effects.

Enhancing Conscious Awareness and Attention

The effects of TBS to the visual and occipital cortex are also difficult to confidently predict, particularly given the delicate balance of excitation and inhibition between regions and between the hemispheres that helps control perception and attention. Applications of cTBS to the occipital cortex have occasionally produced improvements in conscious awareness, visual perception, and visual attention, presumably by mechanisms involving suppression of neural noise to enhance signal-to-noise ratios [24, 54•, 55]. For instance, offline cTBS to V1 increased conscience detection of a target that briefly increased in luminance and was embedded among luminance noise [54•]. This study also found cTBS increased visual cortex GABA concentrations as measured by magnetic resonance spectroscopy, suggesting cTBS increased inhibition in the visual cortex. The authors suggest conscious awareness of target stimuli was enhanced by cTBS-induced suppression of the luminance noise, leading to better signal-to-noise ratios of neural activity underlying conscious vision.

A pair of recent experiments examined visual area middle temporal (MT)/V5's role in feature-based attention, finding both cTBS and iTBS protocols can enhance feature-based attention. In a modified cTBS study, 20 s of offline MT stimulation improved performance in a visual search task where targets were defined by a conjunction of features (color and orientation; [56]). In contrast, cTBS to dlPFC impaired performance. While the dlPFC results are consistent with theories about working memory and memory in visual search [57, 58], the behavioral effects following MT stimulation are surprising as this region is generally tuned for processing motion and is color insensitive. The authors speculate MT disruption could have lessened inhibition of other regions important for color and orientation perception, like V4. However, global feature-based enhancement effects are thought to spread throughout the visual hierarchy [59] and color-based enhancement has been found in MT [60, 61]. It is thus possible that MT is directly involved in feature-based attention.

Supporting this interpretation, a concurrent EEG-iTBS study targeting right MT/V5 also found enhanced feature-based attention [24]. In this case, iTBS increased participants' attention to target-colored, task-irrelevant checkerboards in the periphery, leading to a reduction in the behavioral detection of centrally presented targets. These results indicate modifying MT activity can enhance feature-based attention. The study's EEG data also add to the evidence that TBS effects in the motor cortex might not translate to other cortical regions. This study used flickering stimuli, frequency-tagging task-relevant stimuli, and task-irrelevant peripheral checkerboard distractors at distinguishable frequencies. Flickering stimuli generate steady-state evoked potentials (SSVEPs) at the driving frequencies in the visual cortex, and SSVEP amplitudes increase when attention is directed towards the driving stimuli (e.g., [62]). Globally, iTBS reduced SSVEP amplitudes. Ignored target-colored peripheral distractors showed increased SSVEP amplitudes with stimulation, consistent with feature-based enhancement of the target color. iTBS to right MT also increased the amplitude of attention shifts to right hemifield targets and decreased the amplitude to left hemifield targets, suggesting iTBS could have been inhibiting the right MT rather than exciting it. While these results are not definitive inhibition versus excitation measures, they are nonetheless difficult to explain based on a simple framework of iTBS facilitating cortical excitation.

The evidence on whether TBS can improve higher-level attentional functions, like executive attention or attentional orienting, is sparse. Administering cTBS to different regions within the dorsal frontoparietal attention network produced both impairments and improvements in various attentional functions, presumably by altering the interhemispheric competition between the frontal and parietal regions ([63], see also [64]). Altogether, whether TBS can improve higher-level attentional functions in healthy adults is an understudied topic and more research in this area is needed.

Effects of TBS on Other Cognitive Functions

Beyond the effects described above, pro-cognitive TBS effects have also been observed in two other domains worth noting: speech repetition and reinforcement learning. In a study examining the role of left posterior inferior frontal gyrus (pIFG) in speech repetition, healthy German-speaking participants performed a speech repetition task involving Japanese sentences before and after being administered 600 pulses of

iTBS, cTBS, or an intermediate form of TBS (5 s train of TBS repeated every 15 s) to pIFG [65]. iTBS significantly improved participants' ability to accurately repeat the sentences, while cTBS showed no behavioral effects, and intermediary TBS showed mild improvements in accuracy. As the total number of TBS pulses was the same across conditions, these data are a particularly good example of how the varying delivery patterns of the different TBS protocols can produce very different effects on behavior.

In an interesting cTBS-fMRI study, healthy individuals received cTBS to the left or right dlPFC and then underwent an fMRI scan while they performed a probabilistic reinforcement learning task with positive and negative feedback cues [66••]. Right dlPFC stimulation pushed participants towards a strategy of avoiding negative feedback. In contrast, left dlPFC stimulation biased participants towards reward-guided learning strategies. The fMRI data also indicated left dlPFC stimulation enhanced striatal prediction error coding. Given that cTBS to the left dlPFC can increase striatal dopamine release (e.g., [67]), these results suggest left dlPFC stimulation triggered increased dopamine release in ventral striatum, enhancing participants' reward sensitivity and biasing them towards reward-guided learning strategies.

Clinical Applications

The pro-cognitive effects seen following TBS in healthy individuals grant promise to the use of TBS to ameliorate cognitive impairments in special populations like healthy older adults [43••, 51•, 68], patients with lesions or brain injuries [69, 70], or patients with neuropsychiatric or neurodegenerative disorders ([71–73]; see also [74] for a review of the broader noninvasive stimulation literature). The pro-cognitive effects of TBS in spatial neglect patients and in patients with major depression disorder (MDD) are best demonstrated and are discussed now in more detail.

Spatial Neglect Patients

By altering the balance of interhemispheric inhibition in the posterior parietal cortex (PPC), cTBS to the right PPC can produce spatial attention deficits in healthy individuals that are akin to classic visual neglect symptoms [32•, 75•]. In neglect patients, the unilateral PPC lesions create pathological hyperexcitability within the intact contralesional PPC. By decreasing this hyperexcitability, cTBS over the contralesional PPC has been shown to alleviate spatial attention impairments in neglect patients [70, 76••, 77, 78]. TBS-induced rescuing of spatial attentional performance has been found to persist for days [78] or even weeks [77] after treatment. Spatial attention impairments in neglect are typically increased under high attentional loads, such as when an increasing number of distractor stimuli are presented. A recent study found cTBS to PPC in neglect patients could improve overt visual search performance under both low and high attentional loads [76••]. These results are striking, as cTBS not only improved performance in the low load condition but also produced even larger ameliorative effects in the high load condition, equating target detection performance across loads. These studies thus indicate cTBS is a particularly promising treatment for the symptoms of spatial neglect.

Depression

rTMS to dlPFC is an FDA-approved treatment for mood symptoms in medication-resistant MDD [79]. TBS may also be a useful protocol for treating MDD and could even be more beneficial than standard rTMS treatments [69, 71, 80•, 81]. Given that dlPFC is widely implicated in a host of executive, attentional, and memory functions [82], it is reasonable to predict dlPFC stimulation could also treat cognitive impairments in MDD. The available literature on rTMS improving cognitive function in MDD has produced mixed results (see [74] for review). However, a 2015 study did find pro-cognitive effects following TBS treatment [80•]. Two weeks of iTBS treatment to the left dlPFC in depressed patients significantly improved patients' executive function capabilities, as measured by the Wisconsin Card Sorting Task. These executive function benefits were dissociable from antidepressant responses to TBS and were not observed in patient groups receiving cTBS, combined cTBS/iTBS treatments, or sham stimulation. It is thus possible that TBS treatments for MDD can also improve MDD patients' cognitive functioning, although more research in this area is highly warranted.

Conclusions

In conclusion, TBS protocols have been shown to improve a range of cognitive functions. While high-frequency rTMS and tDCS protocols may also benefit cognitive performance [83], TBS shows particular promise for producing relatively long-lasting effects on behavior with short stimulation times. For instance, ~3 min of TBS can produce behavioral improvements that persist 1 h to 1 day after stimulation. Critically, the growing literature is helping to map the TBS parameter space, expanding what is known about how TBS affects cortical dynamics in different regions. Future studies that combine TBS with neuroimaging methods will be particularly useful for understanding how TBS can affect neural functioning. While more work in healthy controls is needed to further elucidate pro-cognitive effects, TBS does show promise for reliably improving cognitive function in clinical populations. Future work employing patient populations could benefit from including multiple stimulation conditions and probing

for cognitive effects at multiple time points following stimulation, as these results will be of high value for evaluating the immediate and long-term effects of different TBS protocols.

Compliance with Ethical Standards

Conflict of Interest Dr. Elise Demeter declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

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- • Of importance
- •• Of major importance

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