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Review

Concurrent TMS to the primary motor cortex augments slow motor learning

Shalini Narayana [a,b,c,*], Wei Zhang [c], William Rogers [c], Casey Strickland [d], Crystal Franklin [c], Jack L. Lancaster [c], Peter T. Fox [c,e]

[a] Division of Clinical Neurosciences, Department of Pediatrics, University of Tennessee Health Science Center, Memphis, TN, USA
[b] Neuroscience Institute, Le Bonheur Children's Hospital, Memphis, TN, USA
[c] Research Imaging Institute, University of Texas Health Science Center, San Antonio, TX, USA
[d] Department of Psychology, Florida State University, Tallahassee, FL, USA
[e] Audie L. Murphy South Texas Veterans Administration Medical Center, San Antonio, TX, USA

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ABSTRACT

Transcranial magnetic stimulation (TMS) has shown promise as a treatment tool, with one FDA approved use. While TMS alone is able to up- (or down-) regulate a targeted neural system, we argue that TMS applied as an adjuvant is more effective for repetitive physical, behavioral and cognitive therapies, that is, therapies which are designed to alter the network properties of neural systems through Hebbian learning. We tested this hypothesis in the context of a slow motor learning paradigm. Healthy right-handed individuals were assigned to receive 5 Hz TMS (TMS group) or sham TMS (sham group) to the right primary motor cortex (M1) as they performed daily motor practice of a digit sequence task with their non-dominant hand for 4 weeks. Resting cerebral blood flow (CBF) was measured by $H_2^{15}O$ PET at baseline and after 4 weeks of practice. Sequence performance was measured daily as the number of correct sequences performed, and modeled using a hyperbolic function. Sequence performance increased significantly at 4 weeks relative to baseline in both groups. The TMS group had a significant additional improvement in performance, specifically, in the rate of skill acquisition. In both groups, an improvement in sequence timing and transfer of skills to non-trained motor domains was also found. Compared to the sham group, the TMS group demonstrated increases in resting CBF specifically in regions known to mediate skill learning namely, the M1, cingulate cortex, putamen, hippocampus, and cerebellum. These results indicate that TMS applied concomitantly augments behavioral effects of motor practice, with corresponding neural plasticity in motor sequence learning network. These findings are the first demonstration of the behavioral and neural enhancing effects of TMS on slow motor practice and have direct application in neurorehabilitation where TMS could be applied in conjunction with physical therapy.

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* Corresponding author at: Division of Clinical Neurosciences, Department of Pediatrics, 51, North Dunlap Street, Suite 320, Memphis, TN 58105, USA. Fax: +1 901 287 6770.
E-mail address: snaraya2@uthsc.edu (S. Narayana).

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Introduction

Transcranial magnetic stimulation (TMS) is a sub-type of a well-established modality, i.e. electromagnetic stimulation of excitable tissues, and provides a non-invasive alternative to direct electrical stimulation. Since Barker et al.'s (1985) first successful application of TMS in humans, investigators using TMS have published more than ten thousand peer-reviewed publications including more than 1100 in 2009 (http://www.webofknowledge.com, topic = “TMS” search). As a culmination of this extensive body of investigation, the Food and Drug Administration has approved TMS for two indications (therapeutic use in major depressive disorder (MDD) and diagnostic use in pre-surgical mapping), with additional clinical indications in advanced stages of validation (Slotema et al., 2010).

The TMS induced Hebbian alterations in synaptic efficacy (1976), including both long-term potentiation (LTP) and long-term depression (LTD) (Bütefisch et al., 2004) are thought to be the cause of its therapeutic effects. In light of this, it is somewhat surprising that the current emphasis is on the use of TMS alone as a treatment tool, while its uses as an adjuvant with other Hebbian, learning-based interventions are few. For example, TMS is being used as a sole treatment in various psychiatric disorders including MDD, schizophrenia, and anxiety disorder. TMS adjuvancy chiefly has been explored in the context of short-term motor learning (hours to few days) in normal subjects (Boyd and Linsdell, 2009; Bütefisch et al., 2004; Jung and Ziemann, 2009; Kim et al., 2004). However, to date, the effects of TMS over longer periods of motor practice (weeks) have not been examined.

To explore the adjuvant effects of TMS, we used as a model treatment the well-established, highly reliable skill acquisition paradigm introduced by Karni et al. (1995, 1998), and Ungerleider et al. (2002). The Karni paradigm is a regimen of daily repetition (typically 15 min per day) of a five-stroke digit-movement sequence. The skill acquisition in this paradigm is a classic example of Hebbian learning in both behavioral and neurophysiological domains. Thus, it shares with TMS a common mechanism of inducing neural plasticity (Bütefisch et al., 2000; Rioult-Pedotti et al., 1998). In a series of published studies, we and others have demonstrated changes in behavior as well as neuronal properties such as cerebral blood flow and connectivity following slow motor practice (Doyon and Benali, 2005; Karni et al., 1995; Ma et al., 2010, 2011; Xiong et al., 2009). Over the course of weeks, performance scores (typically measured as the number of correct sequences per unit time per session) increase monotonically to an asymptote. Such a time course of learning (~4 weeks) is comparable to the typical durations used in cognitive, behavioral, physical, and speech therapies. This 4-week approach gives this learning paradigm a much greater translational relevance than the single-session learning paradigms typically used in neuroimaging and TMS studies.

Neural systems mediating the incremental skill acquisition following digit sequence practice (DSP) have been outlined by a series of imaging studies in humans using both PET and fMRI (Doyon and Benali, 2005; Duff et al., 2007, 2008; Grafton et al., 1992, 2002; Karni et al., 1995, 1998; Ma et al., 2010, 2011; Poldrack, 2000; Ungerleider et al., 2002; Xiong et al., 2009). Brain regions engaged during slow skill learning include the primary motor cortex (M1), premotor cortex, supplementary motor area (SMA), caudate, putamen, mesial temporal areas including hippocampus, and cerebellum (Doyon and Benali, 2005; Doyon et al., 2009; Ma et al., 2010, 2011; Orban et al., 2011; Xiong et al., 2009). These regions broadly fall under two main networks, the cortico-cerebellar and the cortico-striatal networks. M1 being common to both the networks, is therefore critically involved in skill learning. Thus, due to the role it plays throughout learning, its connections to other brain regions are important in motor learning, and its easy accessibility makes M1 an ideal target site for TMS modulation.

The most common imaging metric used in examining the neural correlates of DSP is the conditional contrast analysis (task minus control) that detects changes in activation patterns. However, no consensus has emerged on the pattern or direction (positive or negative) of the changes associated with motor learning. For example, different groups reported: continued increases in cerebral blood flow in motor areas (Karni et al., 1995, 1998; Ungerleider et al., 2002); a waxing and waning pattern of initial increases followed by a return to baseline (Hlustík et al., 2004; Xiong et al., 2009); and decreases (Poldrack, 2000). As a way to resolve these inconsistent results obtained by the traditional activation approach, our group examined changes in control state i.e., resting cerebral blood flow (CBF) during motor skill acquisition. We found that resting CBF rose significantly during a four-week course of treatment using the Karni slow-learning paradigm (Xiong et al., 2009). In this study, increases in activation (task-minus-rest contrast) were observed prior to the resting CBF changes. Once the resting CBF changes were induced, the activation pattern returned to baseline. These findings were inferred to be the result of a baseline accommodation to the neural demands of intense, daily skill rehearsal. Resting CBF measurement therefore is