Neuroscience 333 (2016) 132–139

MOTOR CORTICAL PLASTICITY IN EXTRINSIC HAND MUSCLES IS DETERMINED BY THE RESTING THRESHOLDS OF OVERLAPPING REPRESENTATIONS

J. L. MIRDAMADI, L. Y. SUZUKI AND S. K. MEEHAN *

School of Kinesiology, University of Michigan, Ann Arbor, MI, USA

Abstract—Knowledge of the properties that govern the effectiveness of transcranial magnetic stimulation (TMS) interventions is critical to clinical application. Extrapolation to clinical populations has been limited by high inter-subject variability and a focus on intrinsic muscles of the hand in healthy populations. Therefore, the current study assessed variability of continuous theta burst stimulation (cTBS), a patterned TMS protocol, across an agonist–antagonist pair of extrinsic muscles of the hand. Secondarily, we assessed whether concurrent agonist contraction could enhance the efficacy of cTBS. Motor evoked potentials (MEP) were simultaneously recorded from the agonist flexor (FCR) and antagonist extensor (ECR) carpi radialis before and after cTBS over the FCR hotspot. cTBS was delivered with the FCR relaxed (cTBS-Relax) or during isometric wrist flexion (cTBS-Contract). cTBS-Relax suppressed FCR MEPs evoked from the FCR hotspot. However, the extent of FCR MEP suppression was strongly correlated with the relative difference between FCR and ECR resting motor thresholds. cTBS-Contract decreased FCR suppression but increased suppression of ECR MEPs elicited from the FCR hotspot. The magnitude of ECR MEP suppression following cTBS-Contract was independent of the threshold-amplitude relationships observed with cTBS-Relax. Contraction alone had no effect confirming the effect of cTBS-Contract was driven by the interaction between neuromuscular activity and cTBS. Interactions across muscle representations should be taken into account when predicting cTBS outcomes in healthy and clinical populations. Contraction during cTBS may be a useful means of focusing aftereffects when differences in baseline excitability across overlapping agonist–antagonist cortical representations may mitigate the inhibitory effect of cTBS.

Key words: theta burst stimulation, transcranial magnetic stimulation, plasticity, motor cortex, flexor carpi radialis, contraction.

INTRODUCTION

The motor cortex is capable of rapid and persistent activity dependent reorganization, known as ‘‘neural plasticity”. The reorganization results from the strengthening of relevant synaptic efficacy via long-term potentiation and/or the weakening in efficacy of task-irrelevant synapses via long-term depression (Sanes and Donoghue, 2000; Cardenas-Morales et al., 2010). Long-term potentiation and long-term depression are critical neural processes in the acquisition and retention of motor skills in healthy individuals as well as the recovery of functional motor ability (Hadj Tahar et al., 2004). However, the changes induced by experience alone require extensive, time intensive interventions (Birkenmeier et al., 2010). As a result, methods to increase neural plastic response have been an area of interest.

Non-invasive brain stimulation applied to the motor cortex can alter neurophysiology and motor performance (Muellbacher et al., 2002). The plastic changes induced by brain stimulation are mechanistically similar to the long-term potentiation and long-term depression that underlie motor learning (Censor and Cohen, 2011). One variant of non-invasive transcranial magnetic stimulation, theta burst stimulation, has been of particular interest given its relative efficiency and long-lasting aftereffects (Huang et al., 2005). However, the benefits of magnetic stimulation in the recovery of motor deficits are moderate (Hsu et al., 2012) and characterized by variability within and across studies (Di Pino et al., 2014).

For intrinsic muscles of the hand the efficacy of both intermittent (iTBS) and continuous (cTBS) theta burst stimulation has been linked to the differential recruitment of intracortical networks rather than inherent differences in the potential for plasticity across individuals (Hamada et al., 2013). However, relatively little research has studied variability of transcranial magnetic stimulation induced aftereffects in the extrinsic muscles of the hand, such as the wrist flexors and extensors. Relative differences in corticospinal control (Fetz and Cheney, 1980; Palmer and Ashby, 1992; Park et al., 2004) and/or stimulation specific transcranial magnetic parameters (Mirdamadi et al., 2015) may determine which intracortical networks are most readily recruited from overlapping cortical representations at the site of stimulation.

The current study sought to assess the effect of cTBS over the FCR cortical hotspot upon the overlapping cortical representations of the FCR and ECR muscles. Consistent with a common underlying mechanism mediating both forms of TBS-induced plasticity (Huang et al., 2011; Hamada et al., 2013) and our previous work using iTBS (Mirdamadi et al., 2015) we hypothesized that

*Corresponding author. Address: University of Michigan, 401 Washtenaw Avenue, Ann Arbor, MI 48109, USA. Fax: +1-734-936-1925.
E-mail address: skmeehan@umich.edu (S. K. Meehan).

http://dx.doi.org/10.1016/j.neuroscience.2016.07.015
0306-4522/

individuals with FCR thresholds that were lower or in close proximity to their ECR threshold would demonstrate stronger suppression of FCR MEPs post-cTBS. Similarly, we hypothesized that individuals with FCR thresholds that were increasingly greater than their ECR threshold would demonstrate progressively stronger suppression of ECR MEPs. Finally, we sought to determine whether intrinsic depolarization associated with isometric FCR contraction could selectively bias cTBS aftereffects to either the agonist or antagonist muscle regardless of relative resting thresholds. In intrinsic hand muscles, the suppressive effect of cTBS over a muscle's motor cortical representation is mitigated by concurrent contraction of that muscle (Huang et al., 2008). Given reciprocal changes in input–output curves of the FCR and ECR during motor skill learning (Suzuki et al., 2012) we hypothesized that concurrent contraction of the FCR (10% of maximum voluntary force) during cTBS would interfere with the buildup of long-term depression-like effects in the FCR muscle and favor suppression of ECR MEP amplitude.

EXPERIMENTAL PROCEDURE

Participants

Fifteen healthy individuals (six males, nine females, 22 ± 4.7 years) participated in Experiment 1. An independent sample of thirteen healthy individuals (three males, 10 females, 21 ± 1.5 years) were recruited to participate in a separate control condition (Experiment 2). All participants provided informed consent; the Institutional Review Board of the University of Michigan Medical School (IRBMED) approved the study protocol.

Experimental design and procedure

For Experiment 1, the same participants completed two testing sessions separated by three days. At each session MEPs were simultaneously recorded from the FCR and ECR muscles in response to single pulses of transcranial magnetic stimulation before and 10, 20 and 30 min after application of cTBS over the FCR cortical hotspot (Fig. 1). Sixteen single pulses were delivered over both the FCR (120% of FCR resting motor threshold) and ECR (120% of ECR resting motor threshold) cortical hotspots. The two testing sessions only differed by the state of the FCR muscle during cTBS. For Session 1, the FCR was relaxed. For Session 2, subjects maintained an isometric contraction of the FCR with the wrist in a flexed position. Isometric contraction was set to 10% of maximum voluntary force. Visual feedback regarding force was provided on a computer screen in front of the participant. Session and order of hotspot stimulation were counterbalanced across participants. Experiment 2 was similar to Experiment 1, except that an independent sample of participants was recruited to complete a session involving isometric wrist flexion in the absence of cTBS (Fig. 1). The effect of isometric wrist flexion in this independent sample was subsequently compared to that of cTBS paired with isometric wrist flexion from the original cohort in Experiment 1.

Stimulation and recording

Transcranial magnetic stimulation was delivered using a MagVenture MagPro X100 with option stimulator (MagVenture Inc., Atlanta, GA) and a statically cooled figure-8 coil (MCF-B70). The coil was oriented tangentially to the scalp over the left motor cortex with the handle at 45° to the midline in a posterior lateral orientation. Surface electromyography was recorded using LabChart 7 software in conjunction with a Dual BioAmp and PowerLab 8/30 acquisition system (AD Instruments, Colorado Springs, CO). Surface electromyography recording was triggered using a 5 V TTL pulse with an epoch of −0.3 to 0.5 s. During acquisition, data were amplified (×1000), digitized (×40,000 Hz) and filtered (band pass filtered 5–1000 Hz, notch filter – 60 Hz). Surface electromyography data were subsequently down-sampled to 5000 Hz during offline analysis.

The FCR and ECR motor cortical hotspots were localized separately. The hotspot for each muscle was defined as the position that elicited the largest MEP in the targeted contralateral muscle. The position of the coil on the scalp for each motor cortical hotspot was recorded using the BrainSight™ stereotactic system (Rogue Research, Montreal, QC). Resting motor threshold was defined for both the FCR and ECR hotspots as the percentage of stimulator output that elicited an MEP of $\geqslant$50 μV peak to peak on five out of 10 trials in the relevant muscle. Active motor threshold for the FCR at the FCR hotspot was defined as the percentage of stimulator output that elicited an FCR MEP of $\geqslant$200 μV peak to peak on five out of 10 trials during tonic wrist flexion of 20% of the maximum force production.

cTBS consisted of three pulses presented at 50 Hz, repeated at 5 Hz for 40 s (600 magnetic stimuli total). Intensity was set to 80% of the active motor threshold for the FCR (Huang et al., 2005).

Data analysis

For both experiments the root mean square error for each MEP was calculated 50 ms prior to stimulus onset. Any trials in which root mean square error of either the targeted or non-targeted muscle exceeded 15 μV were excluded from subsequent analysis (Ackerley et al., 2011; Mirdamadi et al., 2015). The mean peak-to-peak amplitude of the MEP was then derived for each combination of Time (pre, T10, T20, T30), Muscle (Targeted, Non-targeted), Hotspot (FCR, ECR) and Session (cTBS-Relax, cTBS-Contract, cTBS-Alone). The targeted muscle was defined by hotspot. For example, FCR was the targeted muscle when single pulses were delivered over the FCR motor cortical hotspot at 120% of FCR resting motor threshold.

For Experiment 1, separate paired *t*-tests were first run to compare pre-cTBS MEP amplitudes across Session for FCR and ECR MEPs elicited from the FCR