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Research article

Agonist contraction during intermittent theta burst stimulation enhances motor cortical plasticity of the wrist flexors

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HIGHLIGHTS

- iTBS effects on MEP_{FCR} amplitude are a function of $RTM_{FCR} - RMT_{ECR}$ difference.
- Concurrent contraction enhanced MEP_{FCR} amplitude distant from the FCR hotspot.
- Metaplastic effects associated with contraction mitigated effects at the FCR hotspot.
- Contraction is a simple method to enhance the efficacy of TBS in proximal muscles.

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ABSTRACT

Differences in cortical control across the different muscles of the upper limb may mitigate the efficacy of TMS interventions targeting a specific muscle. The current study sought to determine whether weak concurrent contraction during TMS could enhance the efficacy of intermittent theta burst stimulation (iTBS) in the forearm flexors. Motor evoked potentials (MEP) were elicited from the flexor (FCR) and extensor carpi radialis (ECR) motor cortical hotspots before and after iTBS over the FCR cortical hotspot. During iTBS the FCR was either relaxed (iTBS-Relax) or tonically contracted to 10% of maximum voluntary force (iTBS-Contract). iTBS-Relax failed to produce consistent potentiation of MEP_{FCR} amplitude. Individuals with a relatively lower RMT_{FCR} compared RMT_{ECR} demonstrated MEP_{FCR} facilitation post-iTBS-Relax. Individuals with relatively higher RMT_{FCR} demonstrated less facilitation and even suppression of MEP_{FCR} amplitude. iTBS-Contract facilitated MEP_{FCR} amplitude but only for MEP_{FCR} evoked from the ECR hotspot. Interactions between overlapping cortical representations determine the efficacy of iTBS. Tonic contraction increases the efficacy of iTBS by enhancing the volume of the cortical representation. However, metaplastic effects may attenuate the enhancement of MEP gain at the motor cortical hotspot. The use of TMS as an adjunct to physical therapy should account for inter-muscle interactions when targeting muscles of the forearm.

1. Introduction

Intermittent theta burst stimulation (iTBS), a variant of repetitive transcranial magnetic stimulation (TMS), can non-invasively induce increases in excitability of the underlying cortex [7]. Increased excitability is mediated through long-term potentiation (LTP) like mechanisms [5]. Given similar mechanisms underlie motor learning there has been great interest in using repetitive TMS to study motor learning in healthy individuals [6] and as an adjunct to physical therapy in clinical populations [21]. However, results in clinical populations have been variable to date. This variability may in part be attributed to null results when pairing repetitive stimulation of distal hand muscles with unfocused physical therapy targeting arm function [22].

The focus on distal muscles of the hand is likely the result of the difficulty in isolating and inducing effects in relatively more proximal muscles of the upper limb [18]. Differences in corticospinal control from distal to proximal muscles of the upper limb, as well as across flexors and extensors within the proximal muscles [19], may mitigate the effects of iTBS through strong flexor-extensor reciprocal interactions at the cortex [23,25]. Therefore, induction of a slightly depolarized state that favors LTP induction [2] may enhance the specificity and efficacy of iTBS after-effects in targeted proximal muscles.

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In distal muscles synaptic state and history can modulate the effects of TMS [11,16,17,24]. Contraction of the first dorsal interosseous (FDI) during TBS has demonstrated to be ineffective at modulating cortical excitability. Whether proximal muscle contraction during iTBS may enhance after-effects of iTBS has not been investigated. Therefore, the current study determined whether tonic wrist flexion would enhance the efficacy of iTBS upon the motor cortical representation of the flexor carpi radialis (FCR).

Motor evoked potentials (MEP) in the FCR and extensor carpi radialis (ECR) were recorded before and after iTBS over the FCR motor cortical hotspot. iTBS was delivered while the FCR was relaxed or contracted to 10% of maximum voluntary force. The FCR and ECR muscles were chosen as (1) flexor motor cortical excitability is suppressed relative to extensors [20] and (2) the FCR is the primary agonist and ECR the primary antagonist during wrist flexion.

It was hypothesized that MEP_{FCR} amplitude enhancement following iTBS with the FCR at rest would be dependent upon the relative baseline cortical excitability of the FCR and ECR. Further, it was hypothesized that tonic wrist flexion during iTBS would enhance both the gain and volume of FCR cortical excitability.

2. Methods

2.1. Participants

Eighteen healthy individuals (7 males, 11 females, 22 ± 3.6 years) participated in Experiment 1. A second independent sample of sixteen individuals (9 males, 7 females, 22 ± 4.0 years) participated in Experiment 2.

All participants provided informed consent. The Institutional Review Board of the University of Michigan Medical School (IRBMED) approved the protocol. Procedures were conducted in accordance with the Declaration of Helsinki.

2.2. Experimental design and procedure

2.2.1. Experiment 1

Participants completed two testing sessions separated by at least 3 days to reduce the potential for carry over effects between sessions. Participants were seated in a semi-reclined chair with their arms resting on a table. The participant's right forearm maintained a semi-pronated position against a hinged apparatus that allowed wrist flexion. Wrist flexion force was measured by a pressure sensor and presented on a visual display in front of participants.

Motor cortical excitability of both the FCR and ECR was quantified simultaneously by recording MEPs elicited by single pulses of TMS before and 10, 20 and 30 min post-iTBS. At each time point 16 single pulses were delivered at 0.2 Hz over the FCR cortical hotspot (120% of FCR resting motor threshold (RMT_{FCR})). 16 additional pulses were delivered over the ECR cortical hotspot (120% of RMT_{ECR}). At each hotspot, 8 of the 16 single pulses were delivered at rest. The other 8 pulses were delivered during a cued discrete flexion-relaxation movement to a target set to 30% of maximum voluntary force. The movement trials ended when participants had maintained the target force for 200 ms. During flexion trials the single pulse TMS stimulus was triggered when participants exceeded 20% of maximum voluntary force. The order of the rest and flexion trials was counterbalanced across participants. Only the data from the single pulses delivered at rest are reported here.

For Session 1 the FCR was relaxed during iTBS (iTBS-Relax). For Session 2 participants contracted their FCR at 10% of maximum voluntary force during iTBS (iTBS-Contract). Session order and the order of hotspot single pulse stimulation were counterbalanced across participants.

2.2.2. Experiment 2

Experiment 2 was similar to Experiment 1, except that: (1) only the tonic flexion session was completed (Contract-Alone) and (2) iTBS was not delivered.

2.3. Stimulation and recording

Surface electromyography (EMG) was recorded using LabChart and a Dual BioAmp coupled to a PowerLab 8/30 acquisition system (AD Instruments, Colorado Springs, CO). EMG recording was triggered using a 5 V TTL pulse with an epoch of −0.3–0.5 s. During acquisition, data were amplified (×1000), digitized (×40000 Hz) and filtered (band pass filtered 5–1000 Hz, notch filter −60 Hz). Digitization at 40000 Hz was used to facilitate detection of a 5 V TTL trigger. During offline analysis EMG data were subsequently down-sampled to 5000 Hz.

TMS 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. The location and trajectory of the FCR and ECR hotspots were marked on a template brain using the BrainSight™ stereotactic system (Rogue Research, Montreal, QC). RMT_{FCR} and RMT_{ECR} were defined as the percentage of stimulator output that elicited an MEP of $\geq$50 μV peak to peak on 5 out of 10 trials at the muscles' hotspot. Active motor threshold (AMT_{FCR}) was defined as the percentage of stimulator output over the FCR hotspot that elicited an $MEP_{FCR} \geq 200$ μV peak to peak on 5 out of 10 trials during tonic wrist flexion (20% of the maximum FCR force production).

iTBS consisted of three pulses presented at 50 Hz, repeated every 200 ms for 2 s at an intensity of 80% of AMT. 2 s bursts were repeated every 8 s for a total of 600 magnetic stimuli over 190 s [14].

2.4. Data analysis

Mean peak-to-peak MEP_{FCR} and MEP_{ECR} amplitude was derived for each combination of time (pre, T10, T20, T30), muscle (targeted, non-targeted) and hotspot (FCR, ECR). The targeted muscle was defined by hotspot. For example, FCR was the targeted muscle when single pulses were delivered over the FCR hotspot.

For each MEP the root mean square (RMS) was calculated 50 ms prior to stimulus onset. Trials in which RMS of either the targeted or non-targeted muscle exceeded 15 μV were excluded from subsequent analysis.

2.4.1. Experiment 1

Separate one-way repeated measures ANOVA were used to assess the efficacy of iTBS-Relax upon MEP_{FCR} and MEP_{ECR} amplitude evoked from the FCR hotspot. The independent variable was time and the dependent variable was raw MEP amplitude.

The relationship between iTBS-Relax after-effect and $RMT_{FCR} - RMT_{ECR}$ difference was assessed using separate Pearson product moment correlations (PPMC) at T10, T20 and T30. MEP amplitude (percentage of pre-iTBS amplitude) and difference between $RMT_{FCR} - RMT_{ECR}$ were the variables of interest.

The effect of concurrent contraction within a muscle but across hotspot was assessed using separate Session (iTBS-Relax, iTBS-Contract) × hotspot × time repeated measures ANOVAs for each Muscle. The dependent variable was MEP amplitude expressed as a percentage of pre-iTBS MEP amplitude. Significant Session × hotspot × time interactions were decomposed using separate Session × time repeated measures ANOVA for each Hotspot.