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Research report

Selective modulation of left primary motor cortex excitability after continuous theta burst stimulation to right primary motor cortex and bimanual training

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HIGHLIGHTS

- Theta burst stimulation (TBS) to right primary motor cortex (rM1) and bimanual training (BMT).
- TBS to rM1 and BMT caused a greater shift in centre of gravity and prolonged increased spatial map.
- TBS to rM1 and BMT individually increased map volume and spatial map.
- Modulation of rM1 with rehabilitation may be useful in enhancing excitability in damaged cortex.

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ABSTRACT

Bimanual movement training (BMT) enhances the excitability of human preparatory premotor and primary motor (M1) cortices. We have shown that activity in M1 is enhanced after BMT involving simultaneous activation of homologous muscles (in-phase). Potential neural mechanisms underlying this effect could be input from premotor areas (i.e. dorsal premotor cortex (PMd)) and/or the homologous M1 representation. Recently, we showed that increasing PMd activity using theta burst stimulation (TBS) followed by BMT enhanced the corticospinal excitability of M1 compared to BMT alone. The purpose of this study was to investigate the effects of continuous TBS (cTBS) to right hemisphere M1 (rM1) on the homologous wrist extensor representation in left M1 (lM1), and its potential combined effects when followed by BMT. We used transcranial magnetic stimulation (TMS) to measure cortical excitability of extensor carpi radialis (ECR) representation at multiple time points in three conditions: (1) BMT, (2) cTBS to rM1 or (3) cTBS to rM1 and BMT. The combination of cTBS to rM1 and BMT resulted in an increased shift in the centre of gravity (CoG) compared to either intervention alone, along with an increased muscle topographical representation up to 60 min when cTBS to rM1 was combined with BMT compared to cTBS to rM1 alone. These results suggest that modulation of M1 may reduce ongoing interhemispheric inhibition (or increase facilitation indirectly) to the opposite homologous M1 region in healthy individuals via transcallosal or subcortical connections. Critically, this work may guide rehabilitation training and stimulation techniques that modulate cortical plasticity after brain injury.

1. Introduction

Training upper-limb movements modulates the excitability in several cortical areas, such as motor [1–7], premotor (PM) [5,8–13], and parietal cortices as well as subcortical areas including the basal ganglia and cerebellum [14–17]. Critically, bimanual visuomotor movement training (BMT) yields a greater increase in PM [11–13] and primary motor (M1) [18,19] cortical excitability compared to unimanual movement training. Further, in select stroke patients, bimanual movement performed with the upper-limbs, involving both the damaged and undamaged hemisphere, may increase the excitability within the stroke-affected hemisphere [20,21]. Additionally, bimanual arm training has been shown to improve hand and arm function in stroke patients [22–27]. Although BMT can modulate the excitability in motor preparation and execution areas as well as improve upper-limb function in patient populations, the underlying neural mechanisms remain unclear.

Modulation of cortical excitability after BMT likely relates to the phase of movement with some influence of the motor preparatory aspect of the trained movements [18,19]. Specifically, increases in

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motor preparatory and execution areas occur when BMT involves the simultaneous co-activation of homologous muscle groups (in-phase training), but not with co-activation of antagonist muscle groups (anti-phase training) [11–13,18,19]. Electroencephalography (EEG) work suggests that in-phase BMT specifically modulates preparatory activity in PM cortices. More specifically to M1, transcranial magnetic stimulation (TMS) work has shown that in-phase BMT increases M1 excitability, namely, enhancing the size of the excitable topographical representation of the trained muscle [18,19]. Further, a recent work has demonstrated that enhancing excitability in the left PM via intermittent theta burst stimulation (iTBS) before BMT leads to enhanced excitability in M1 compared to either intervention alone, namely, an increase in both the topographical distribution and global MEP amplitudes of the trained muscle representation [19].

A possible mechanism underlying the reported effects of BMT [11–13,18,19] is the interhemispheric interaction between homologous M1 representations. Many animal and human studies indicate that there are extensive reciprocal interhemispheric connections between homologous muscle representations in M1 [28–33]. There are both inhibitory and excitatory connections between the homologous M1 representations, yet inhibition between the hemispheres seems to dominate [29,30,34–36]. Several studies indicate that muscle activation of one limb enhances the excitability of the contralateral homologous muscle representation, a phenomenon known as cross-facilitation [37–39]. Also, local cortical inhibition in M1 is released between homologous M1 representations when the upper-limbs are moved synchronously (in-phase), but inhibition remains during asynchronous (anti-phase) movements [40,41]. Further, interhemispheric inhibition (IHI) from the actively to passively moved limb in M1 is reduced after repetitive in-phase active–passive movement training of the upper-limbs [42]. These studies suggest that interhemispheric connections between M1 representations may be a potential neural mechanism for cross-facilitation, with presumed GABA-mediated local M1 disinhibition, which underlies the corticospinal modulations observed due to bimanual tasks.

TMS has become a useful way to measure and modulate the intracortical and subsequent corticospinal excitability in focal areas of the brain. Repetitive TMS (rTMS) can induce lasting modulations of cortical excitability. A specific type of rTMS, known as theta burst stimulation (TBS) [43] modulates local cortical excitability with a short period of rapid stimulation. Specifically, when continuous theta burst stimulation (cTBS) is applied to M1, amplitudes of motor-evoked potentials (MEPs) from the stimulated M1 are suppressed for up to 60 min post stimulation [43–45], with this effect showing variability across participants, likely depending upon which interneuron populations are activated by the TMS pulse [46]. Additionally, a few studies suggest that cTBS applied to the right hemisphere M1 (rM1) increases corticospinal activity in the left M1 (lM1) [45,47]. Also, motor function of the affected limb improves in stroke patients after applying cTBS to the contralesional M1 or S1 in combination with movement training [48]. Therefore, there is evidence that modulation of M1 representations in one hemisphere can remotely influence excitability of homologous representations in the opposite M1, and that this remote modulation may additively facilitate motor behaviour when followed by a motor training task. Despite these findings, the underlying neural mechanisms and remote cortical nodes (i.e. contralateral homologous M1) contributing to the reported effects due to BMT remain unclear. Furthermore, it is unknown whether the remote modulation of lM1 (cTBS to homologous rM1) will be additive with the cortical excitability changes observed due to BMT [11–13,18,19].

The current study investigates the effect of cTBS to rM1 on the opposite hemisphere M1 (lM1) in terms of the spatial representation and MEP amplitude of the extensor carpi radialis (ECR) muscle over time. Additionally, this study explores the possible combined effects of cTBS to rM1 applied before BMT on lM1 corticospinal excitability. It was hypothesized that cTBS to rM1 would enhance the excitability of the lM1 ECR representation. Also, it was hypothesized that cTBS to rM1 would enhance the excitability in lM1, which will potentially cause a greater enhancement of ECR cortical excitability when followed by BMT.

2. Methods

2.1. Participants

Twenty-seven healthy, self-reported right-handed participants (12 female; average age = 26 ± 4 years) took part in the study. Participants were divided into three groups with different interventions: BMT (group 1) (collected and reported in the previous study [19]), cTBS to rM1 alone (group 2) and cTBS to rM1 followed by BMT (group 3). Ten individuals participated in group 1, while twelve individuals participated in groups 2 and 3 in random order, with five individuals participating in both groups 2 and 3 and these experiments were separated by at least one week. The experimental procedures were approved by the University of Waterloo, Office of Research Ethics. All participants provided informed written consent and completed a TMS screening form [49].

2.2. Electromyographic (EMG) recording

Surface EMG was recorded from the right and left extensor carpi radialis (ECR) muscles using 9 mm diameter Ag–AgCl electrodes. Two active electrodes were placed over the muscle belly of the right and left ECR with a ground electrode over the right styloid process of the ulna. EMG recordings were amplified (2000×), band-pass filtered (20–200 Hz), digitized with a sample frequency of 1 kHz, and stored for later analysis, using customized LabVIEW software (National Instruments, Austin, TX, USA).

2.3. TMS and neuronavigation

Focal TMS and TBS were performed using a MagPro x100 stimulator (Medtronic, Minneapolis, MN, USA) and Figure-8 (MCF-B65) 90 mm stimulation coil. BrainSight Neuronavigation (Rogue Research, Canada) was used to ensure replication of the scalp positions for stimulation of the M1 topographical representation via online tracking of the coil using a template MRI for all participants. The motor hotspot for the ECR in lM1 was acquired by placing the stimulation coil on the scalp at a 45° angle to the mid-sagittal plane. The motor hotspot was determined to be the location in lM1 to elicit an optimal MEP in the contralateral (right) resting ECR. The resting motor threshold (RMT) was defined as the lowest stimulus intensity that would elicit 5 out of 10 consecutive MEPs greater than or equal to a peak-to-peak amplitude of 50 μV [50]. The active motor threshold (AMT) was defined as the lowest stimulus intensity that would elicit 5 out of 10 consecutive MEPs greater than or equal to a peak-to-peak amplitude of 200 μV while maintaining a contraction in the left ECR of 10% of maximum voluntary contraction, while holding the stimulator over the optimal ECR representation in rM1. For cTBS, the theta burst pattern of stimulation (three stimuli delivered at 50 Hz, which were grouped and delivered every 5 Hz) was delivered in continuous blocks for a total of 600 stimuli applied over 40 s [43]. cTBS was delivered to rM1 at 80% of AMT [45,48,51].

The modulation of lM1 excitability was measured using the amplitude and topographical distribution of MEPs elicited by single-pulse TMS over the excitable area occupied by the wrist extensor muscle representation [2,7,18,19,52,53]. The MEP amplitude is an index of cortical and spinal excitability for a particular