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Research report

# Modulation of left primary motor cortex excitability after bimanual training and intermittent theta burst stimulation to left dorsal premotor cortex

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## HIGHLIGHTS

- Intermittent TBS (iTBS) to dorsal premotor cortex (PMd) and bimanual training (BMT).
- iTBS to PMd and BMT caused a concurrent increase in spatial map and global MEP amplitude.
- iTBS to PMd markedly increased global MEP amplitude, and BMT enhanced the spatial map.
- Modulation of PMd with rehabilitation may be useful in enhancing excitability in damaged cortex.

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## ABSTRACT

Bimanual visuomotor movement training (BMT) enhances the excitability of human preparatory premotor and primary motor (M1) cortices compared to unimanual movement. This occurs when BMT involves mirror symmetrical movements of both upper-limbs (in-phase) but not with non-symmetrical movements (anti-phase). The neural mechanisms mediating the effect of BMT is unclear, but may involve interhemispheric connections between homologous M1 representations as well as the dorsal premotor cortices (PMd). The purpose of this study is to assess how intermittent theta burst stimulation (iTBS) of the left PMd affects left M1 excitability, and the possible combined effects of iTBS to left PMd applied before a single session of BMT. Left M1 excitability was quantified using transcranial magnetic stimulation (TMS) in terms of both the amplitudes and spatial extent of motor evoked potentials (MEPs) for the extensor carpi radialis (ECR) before and multiple time points following (1) BMT, (2) iTBS to left PMd or (3) iTBS to left PMd and BMT. Although there was not a greater increase in either specific measure of M1 excitability due to the combination of the interventions, iTBS applied before BMT showed that both the spatial extent and global MEP amplitude for the ECR became larger in parallel, whereas the spatial extent was enhanced with BMT alone and global MEP amplitude was enhanced with iTBS to left PMd alone. These results suggest that the modulation of rapid functional M1 excitability associated with BMT and iTBS of the left PMd could operate under related early markers of neuro-plastic mechanisms, which may be expressed in concurrent and distinct patterns of M1 excitability. Critically, this work may guide rehabilitation training and stimulation techniques that modulate cortical excitability after brain injury.


## 1. Introduction

Visuomotor movement training modulates the excitability in several cortical areas, namely, motor [1–7], premotor (PM) [5,8–13], and parietal cortices as well as subcortical areas such as the basal ganglia and cerebellum [14–17]. In individual stroke patients, bimanual movement performed with the upper-limbs can increase the excitability within the damaged primary motor cortex (M1) [18,19]. Critically, bimanual visuomotor movement training (BMT) yields a greater increase in premotor [11–13] and M1 [20] cortical excitability than does unimanual movement training. Additionally, bimanual arm training has been shown to improve hand and arm function in stroke patients [21–26]. 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 emphasizing the motor preparatory aspect of the trained movements [20]. Specifically,

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increases in 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) [11–13,20]. Electroencephalography (EEG) work suggests that in-phase BMT modulates preparatory activity in PM cortices and possibly M1. This increase in preparation-associated cortical activity was found during the performance of similar unilateral movements not specifically trained [11,12]. Likewise, transcranial magnetic stimulation (TMS) work has shown that in-phase BMT, but not anti-phase, increases M1 excitability. Specifically, the excitable cortical territory of trained muscle representation increases along the borders without a concurrent increase in excitability of the central representation of that muscle [20]. The lack of effect due to anti-phase training may relate to the reciprocal inhibition of active versus inactive agonist and antagonist muscle representations in the contralateral hemispheres [27]. In addition, motor preparation associated with a goal-directed movement during training increases cortical excitability and, in turn, improves behavioural performance [8,10–13,28]. Conversely, without this goal-directed motor preparation, cortical activation is slightly decreased and task performance generally declines [8].

Indeed, behavioural studies have shown that covertly and overtly preparing movements to a target stimulus decreases reaction times (RTs) and increases activity in PM cortices [29–32]. The dorsal premotor cortex (PMd) has well-known roles in the selection of appropriate actions for movement execution [33–36]. Interestingly, neuroimaging and TMS research suggest that PMd in the left hemisphere has an important role in action selection for motor execution [37,38]. Specifically, PMd seems to be particularly involved in movement selection with learned visuomotor associations [38,37]. Also, left PMd activity increases with action selection of one or both upper-limbs [39]. Further, when the right PMd is disrupted with inhibitory TMS, action selection is hindered in the contralateral hand alone. Conversely, disruption of left PMd leads to a disruption in action selection of both upper-limbs [40,41]. Similarly, repetitive TMS to left PMd causes faster preparation of complex sequences performed with the right hand [42]. This suggests that the left PMd has a particularly relevant role in movement selection with both upper-limbs and the learning of visuomotor behavioural associations.

Theta burst stimulation (TBS) is a type of repetitive TMS (rTMS) that has been shown to modulate the cortical excitability of M1 after a brief period of stimulation [43]. Continuous theta burst stimulation (cTBS) decreases cortical excitability of M1, and intermittent theta burst stimulation (iTBS) enhances the excitability of M1 as demonstrated by respective modulations in motor evoked potential (MEP) amplitude. Furthermore, cTBS to PMd decreases MEP amplitude of the ipsilateral M1 representation [44,45]. Subthreshold rTMS to PMd decreases ipsilateral M1 cortical excitability when delivered at 1 Hz, and increases excitability when delivered at 5 Hz [35,46–49]. This suggests that M1 excitability may be differentially modulated by unique stimulation patterns to remote and related areas, like PMd. Specifically, there are strong excitatory anatomical connections between the PM and M1 cortices, particularly within the left hemisphere [50–52]. Therefore, up-regulating the excitability of the left PMd may lead to a modulation in the excitability of the left (ipsilateral) M1. Furthermore, given that PMd has been shown to be specifically involved with action selection of learned associations with both upper-limbs, perhaps enhancing the excitability of ipsilateral PMd via iTBS will lead to a greater enhancement of M1 excitability when combined with BMT compared to BMT alone.

The current study investigates the effect of short-term in-phase BMT, iTBS to left PMd and the possible combined effects of iTBS to left PMd applied before BMT on left M1 cortical excitability. It was hypothesized that in-phase BMT would increase the corticospinal excitable area of left M1. Also, it was hypothesized that iTBS to left PMd would enhance the excitability of the M1. Finally, it was hypothesized that iTBS to left PMd would potentially enhance the excitable input from PMd to the motor cortices and, in turn, enhance M1 corticospinal excitability to a greater extent when followed by BMT.

## 2. Methods

### 2.1. Participants

Twenty healthy, self-reported right-handed participants (seven female; average age = 27 years, range 21–38) took part in the study. Participants were divided into three groups with different interventions: BMT alone (group 1), iTBS to left PMd alone (group 2) and iTBS to left PMd followed by BMT (group 3). Ten individuals participated in each of the three interventions in random order, with no participants performing the bimanual training twice. 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 [55].

### 2.2. Electromyographic (EMG) recording

Surface EMG was recorded from the right extensor carpi radials (ECR) muscle using 9 mm diameter Ag–AgCl electrodes. Two active electrodes were placed over the muscle belly of the ECR with a ground electrode over the 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 & neuronavigation

Focal TMS was performed using a MagPro × 100 stimulator (Medtronic, Minneapolis, MN, USA) and figure-8 (MCF-B65) 70 mm stimulation coil. BrainSight Neuronavigation (Rogue Research, Canada) was used to guide the coil to the cortical target areas using a template MRI for all participants. The motor hotspot for the ECR in M1 of the left hemisphere 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 left M1 to elicit an optimal MEP in the contralateral resting (right) ECR. The resting motor threshold (rMT) was defined as the lowest stimulus intensity that would elicit 5 out of 10 MEPs greater than or equal to a peak-to-peak amplitude of 50 μV [56]. The active motor threshold (AMT) was defined as the lowest stimulus intensity that would elicit 5 out of 10 MEPs greater than or equal to a peak-to-peak amplitude of 200 μV while maintaining a light contraction of the ECR of 10% of maximum voluntary contraction. For iTBS, the theta burst pattern of stimulation (three stimuli delivered at 50 Hz, which were grouped and delivered at 5 Hz) was delivered in blocks of 2 s followed by a period of 8 s with no stimulation, for a total of 600 stimuli applied over 190 s [42,43]. We delivered iTBS to PMd in the left hemisphere [42,44] at 80% of AMT. The location of PMd was determined to be 2.5 cm anterior to the ECR motor hotspot in left M1 [42,44,50].

The modulation of M1 excitability in the left hemisphere was measured using the amplitude and spatial extent of MEPs elicited by single-pulse TMS over the excitable cortical area occupied by the wrist extensor muscle representation [2,7,20,53,54]. The MEP amplitude is an index of cortical and spinal excitability for a particular target muscle while the cortical map of evoked activity indicates the spatial extent of excitability for a given targeted muscle [2,7,20,53,54]. Both of these measures are related, but