Theta Burst Stimulation of Human Primary Motor Cortex Degrades Selective Muscle Activation in the Ipsilateral Arm

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Bradnam LV, Stinear CM, Byblow WD. Theta burst stimulation of human primary motor cortex degrades selective muscle activation in the ipsilateral arm. J Neurophysiol 104: 2594–2602, 2010. First published September 15, 2010; doi:10.1152/jn.00365.2010. This study investigated whether repetitive transcranial magnetic stimulation (TMS) delivered as continuous theta burst stimulation (cTBS) to left M1 degraded selective muscle activation in the contralateral and ipsilateral upper limb in healthy participants. Contralateral motor-evoked potentials (cMEPs) were elicited in left and right biceps brachii (BB) before either elbow flexion or forearm pronation. A neurophysiological index, the excitability ratio (ER), was computed from the relative size of BB cMEPs before each type of movement. Short interval intracortical inhibition (SICI) was assessed in cMEPs of right BB with paired-pulse TMS of left M1. Ipsilateral MEPs (iMEPs) and silent periods (iSPs) were measured in left BB with single-pulse TMS of left M1. Low-intensity cTBS was expected to suppress corticospinal output from left M1. A sham condition was also included. Real but not sham cTBS caused increases in BB ER bilaterally. In the right arm, ER increased because BB cMEPs before flexion were less facilitated, whereas cMEPs in the pronation task were unaffected. This was accompanied by an increase in left M1 SICI. In the left arm, ER increased because BB cMEPs before pronation were facilitated but were unaffected in the flexion task. There was also facilitation of left BB iMEPs. These changes in the left arm are consistent with inappropriate facilitation of left BB α-motoneurons (αMNs) before pronation. This is the first demonstration that cTBS of M1 can alter excitability of neurons controlling ipsilateral proximal musculature and degrade ipsilateral upper limb motor control, providing evidence that ipsilateral and contralateral M1 shape the spatial and temporal characteristics of proximal muscle activation appropriate for the task at hand.

INTRODUCTION

Common upper limb movements such as reaching rely on precise recruitment of proximal and distal musculature. There is a growing body of evidence that both contralateral and ipsilateral primary motor cortex (M1) contribute to skilled execution of unimanual upper limb tasks (Chen et al. 1997; Davare et al. 2007; Duque et al. 2008; Muehlbacher et al. 2000; Perez and Cohen 2008). The role of ipsilateral M1 in upper limb motor control in healthy humans is not well understood. The ipsilateral M1 has a greater influence over proximal than distal upper limb, because outputs project bilaterally to α motoneurons (αMNs) innervating homologous proximal muscles on either side of the body (Kuypers 1964; Lemon 2008). Ipsilateral motor-evoked potentials (iMEPs) from transcranial magnetic stimulation (TMS) have a longer latency than contralateral MEPs (cMEPs) in proximal muscles (Alexander et al. 2007; Bawa et al. 2004; MacKinnon et al. 2004), indicating that iMEPs are mediated by indirect pathways such as the ipsilateral reticulospinal tract or cervical propriospinal system (Chen et al. 2003; Ziemann et al. 1999). Indirect projections from ipsilateral M1 converge onto interneurons in the spinal cord in common with those from the contralateral corticospinal tract (Kuypers 1964; Lemon 2008). This bilateral innervation may contribute to the control of proximal muscles and synergies during upper limb reaching.

The contribution of ipsilateral M1 to proximal upper limb function can be assessed in humans using repetitive TMS (rTMS). Inhibitory rTMS applied to ipsilateral M1 has been found to both improve (Avanzino et al. 2008, 2009; Dafotakis et al. 2008; Kobayashi et al. 2004, 2009), and degrade (Carey et al. 2006; Chen et al. 1997) measures of performance of the ipsilateral hand. Continuous theta-burst stimulation (cTBS) is a pattern of rTMS that suppresses corticospinal output of stimulated M1 (Gentner et al. 2008; Huang et al. 2005; Ishikawa et al. 2007; Stefan et al. 2008; Suppa et al. 2008), and interestingly, increases excitability of homologous representations in the nonstimulated M1 (Iezzi et al. 2010; Ishikawa et al. 2007; Stefan et al. 2008; Suppa et al. 2008). These behavioral and neurophysiological effects of M1 rTMS and cTBS have been attributed to the modulation of interhemispheric inhibition, although this has not been examined directly. This study investigated whether M1 cTBS influences interhemispheric inhibition, ipsilateral projections from the stimulated M1, or both.

Selective muscle activation within the upper limb is essential for skilled manipulation with the hand. In the contralateral motor cortex, facilitation of cortical representations of prime movers is accompanied by inhibition of surrounding muscles to shape fine motor control (Sohn and Hallet 2004; Stinear and Byblow 2003). However, for proximal muscles, there may be a concomitant role for ipsilateral M1 in selective muscle activation via projections to interneurons and αMNs in the spinal cord (Alstermark et al. 1984, 2007; Illert and Tanaka 1978; Illert et al. 1977, 1981; Isa et al. 2006).

Gerachshenko et al. (2008) assessed selective muscle activation in healthy human participants and in patients after stroke. They recorded cMEPs in biceps brachii (BB) using TMS applied before elbow flexion or forearm pronation. The ratio of BB cMEP size before pronation to BB cMEP size before flexion was used to calculate an excitability ratio (ER). Briefly, cMEPs in BB were facilitated before elbow flexion, when BB acts as an agonist, and suppressed before forearm pronation, when BB acts as an antagonist. In healthy subjects,
a small ER is expected. Chronic stroke patients with impaired upper limb control exhibit a high ER (Gerachshenko et al. 2008), showing its potential utility as a neurophysiological measure of selective muscle activation in the proximal upper limb.

In this study, we calculated in healthy participants the ER of both ipsilateral and contralateral arms before and after low-intensity cTBS presumed to suppress output from left M1 (McAllister et al. 2009). Because of the bilateral innervation of proximal upper limb muscles, we hypothesized that cTBS of left M1 would degrade selective activation of BB in the contralateral and ipsilateral upper limb, detected by an increase in ER. We also examined iMEPs and ipsilateral silent periods (iSPs) in left BB and short-latency intracortical inhibition (SICI) from right BB cMEPs, to explore possible mechanisms for any effects of cTBS on selective activation of BB.

METHODS

Participants

Nine healthy adults (mean age, 26 ± 2.5 yr; range, 21–45 yr; 2 males) without history of upper limb neurological or musculoskeletal disorder completed the study. Participants were screened for contralective indications to TMS by a neurologist. All were right handed (range, +68 to +100; mean ± 91), assessed by the Edinburgh Handedness Inventory (Oldfield 1971). Informed consent was given by all participants in accordance with the Declaration of Helsinki, and the study was approved by the local ethics committee.

Experimental design

Participants completed three experimental sessions, separated by at least 5 days. The intervention, cTBS or sham cTBS, was delivered to left M1 in every session. In two sessions, cTBS was delivered to left M1, and in one session, sham cTBS was delivered to left M1. Paired-pulse TMS was used to assess SICI in left M1 in all three sessions. The three sessions differed in the hemisphere stimulated with single-pulse TMS and the arm/s used to perform motor tasks. The session protocols and measures are identified in Table 1. Note that Right and Left refer to the arm engaged in the motor task. cTBS or sham TBS was delivered to left M1 in all three sessions. In the Right/Left sham session, tasks were performed first by one, and then the other arm, in a randomized order. Participants were informed the intent was to compare a bilateral task to the unilateral task in Right cTBS and Left cTBS sessions. The aim was to divert attention away from the sham session, although as a result the experimenter was not blinded. A potential limitation of this design was that tasks performed in Right/Left sham differed from Right cTBS and Left cTBS in the number of pre- and postintervention measurements but was not expected to have a bearing on any outcome measure.

Motor tasks

Participants performed two rhythmic motor tasks while seated with their hand positioned around an upright handle and the forearm constrained to prevent unintended movement. Participants were instructed not to grip the handle and to isolate their movements to the elbow or forearm. The flexion task involved isometric elbow flexion, whereas the pronation task involved isometric forearm pronation. Flexion and pronation contractions were paced with an auditory metronome, initially set at 1 Hz and adjusted to a comfortable tempo, if required, for the individual (mean frequency, 0.9 ± 0.1 Hz). This allowed participants to keep pace with the metronome as precisely possible and to relax completely between each contraction. Fifty repetitions were performed in blocks, with no more than 2-min rest between blocks as required. No more than six blocks of 50 repetitions were collected for each task depending on task performance.

EMG

Surface EMG was recorded from the long head of the right and left BB, just proximal to the musculotendinous junction and the right and left pronator teres (PT). Disposable adhesive electrodes (30 × 20 mm, Ambu, Ballerup, Denmark) were positioned over the muscle bellies, 1 cm apart in a bipolar montage. EMG signals were amplified (CED 1902), bandwidth filtered (20–1,000 Hz), and sampled at 2 kHz (CED 1401).

MEPs

TMS was delivered with a figure-of-eight coil (70-mm wing diam), connected to two MagStim 200 stimulators via a MagStim Bistim unit (MagStim, Whitland, Dyfed, Wales). The coil was positioned over M1, with the handle pointing posterolaterally at a 45° angle, to induce a current directed posterior to anterior in the underlying tissue. The hotspot for eliciting cMEPs in contralateral BB was located and marked on the scalp with a colored pen. Active motor threshold (AMT) was defined as the minimum stimulus intensity that elicited a 100-μV MEP in 5 of 10 trials during a BB contraction. AMT was determined using 1% maximal stimulator output (MSO) step-widths. Single-pulse TMS was delivered to either left M1 (Right cTBS and Right sham sessions) or right M1 (Left cTBS and Left sham sessions) at 120% AMT. Twelve trials were first recorded with the target BB at rest to confirm that this stimulus intensity was below rest motor threshold (Gerachshenko et al. 2008). TMS was delivered 50–250 ms before the auditory metronome signaled the onset of muscle activity to occur (Signal, CED, Cambridge, UK). The range in timing between TMS and metronome compensated for interindividual variations in task performance. BB cMEPs were recorded in blocks of 10 for each task. Between 30 and 50 cMEPs were collected for each task to ensure an adequate number of trials without prestimulus EMG for subsequent analysis.

Paired-pulse TMS was used to assess SICI in left M1 at each session using the method described by Kujirai et al. (1993). A subthreshold conditioning stimulus, delivered 3 ms before the test TMS stimulus, was used to preferentially excite M1 intracortical inhibitory interneurons, and the subsequent reduction in cMEP amplitude compared with the nonconditioned cMEP provided a measure of SICI. Participants sat quietly, their hands resting on a cushion with forearms supinated. Nonconditioned cMEP stimulus intensity was adjusted to evoke the largest cMEP possible for each individual in the right BB at rest. Resting thresholds are higher in proximal muscles

### TABLE 1. Session protocols and measures

<table>
<thead>
<tr>
<th>Session</th>
<th>Intervention</th>
<th>Paired-Pulse TMS</th>
<th>Single-Pulse TMS</th>
<th>Motor Tasks</th>
</tr>
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<tbody>
<tr>
<td>Right cTBS</td>
<td>cTBS left M1</td>
<td>Left M1</td>
<td>Left M1</td>
<td>Right arm</td>
</tr>
<tr>
<td>Left cTBS</td>
<td>cTBS left M1</td>
<td>Left M1</td>
<td>Right M1</td>
<td>Left arm</td>
</tr>
<tr>
<td>Right/Left sham cTBS</td>
<td>Sham left M1</td>
<td>Left M1</td>
<td>Left M1/Right M1</td>
<td>Right arm/Left arm</td>
</tr>
</tbody>
</table>

TMS, transcranial magnetic stimulation; M1, primary motor cortex; cTBS, continuous theta burst stimulation.
than distal muscles, as reflected in the amplitude of the nonconditioned right BB cMEP (average, 0.34 ± 0.03 mV). The conditioning stimulus (CS) was delivered at a range of intensities (70, 85, and 100% of right BB AMT) to construct a SCI recruitment curve (Peurala et al. 2008). Ten nonconditioned cMEPs and 10 conditioned cMEPs, at each intensity, were collected in randomized order at a rate of 0.2 Hz.

To evoke iMEPs and iSPs in left BB, 16 single-pulse stimuli were delivered to left M1 at 80% MSO. This intensity was chosen as it was found previously to most consistently evoke iMEPs in proximal muscles in healthy adults (Bradnam et al. 2010). The same coil position and orientation was used as that to elicit cMEPs. Stimuli were delivered at a rate of 0.2 Hz while participants performed an isometric left BB contraction with a rest between stimuli.

**TBS**

cTBS was delivered to left M1 with a Rapid Stimulator (MagStim). Participants sat quietly with their hands resting on their lap. A flat figure-of-eight coil (75-mm wing diam) was positioned over the left M1 BB hotspot. AMT was determined for right BB using the Rapid Stimulator. cTBS was delivered at 70% of right BB AMT. This intensity has been shown to specifically target intracortical neurons within the superficial layers of M1 (McAllister et al. 2009). The cTBS protocol consisted of triplets of stimuli (interstimulus interval, 20 ms), delivered every 200 ms to total 600 pulses (Huang et al. 2005). Sham cTBS was delivered through a flat figure-of-eight sham coil positioned as for cTBS. The intensity was set to 80% AMT to provide some sensory stimulation and discharge noise without affecting the underlying cortical tissue, to ensure participants remained blinded to the sham intervention. After stimulation, participants sat quietly with eyes closed for 5 min to consolidate effects.

**Data analysis**

BB cMEPs and root mean square EMG. EMG traces were visually inspected, and only trials with TMS delivered before voluntary muscle activation were accepted for analysis (Gerachshenko et al. 2008). The time to agonist muscle EMG onset (BB before flexion, PT before pronation) after the stimulus was calculated. Trials where the time to agonist onset was >200 ms were discarded because the facilitation and suppression of BB cMEPs before movement occur within this window (Gerachshenko and Stinear 2007). Prestimulus root mean square EMG (rmsEMG) was calculated (~100 to ~1 ms) and sorted so that the difference in the mean rmsEMG between stimulation and pronation trials was <2 SD. Average BB cMEP amplitude was determined for both tasks from the retained trials. The number of cMEPs in the average differed for each individual, ranging between 12 and 35 for flexion and between 15 and 38 for pronation. The latency of the BB cMEP was calculated from flexion trials, because cMEPs were more consistently evoked than in pronation trials. Latency was measured at the first deflection from baseline in a window 10–25 ms after the stimulus artifact. The change in BB cMEP amplitude was calculated by subtracting the mean pre-TBS amplitude from the mean post-TBS amplitude and expressing this as a percentage of the mean pre-TBS amplitude for each participant. Average BB MEP amplitude before pronation was expressed as a ratio of the average BB MEP amplitude before flexion to calculate an excitability ratio (ER) before and after cTBS (Gerachshenko et al. 2008).

BB ER and cMEP latencies were analyzed with a 2 STIMULATION (cTBS, Sham cTBS) × 2 SIDE (Right, Left) × 2 TIME (Pre, Post) repeated-measures ANOVA (rmANOVA) (Table 2). Change in BB cMEP amplitude was analyzed using a 2 TASK (Flexion, Pronation) × 2 STIMULATION (cTBS, Sham cTBS) × 2 TIME (Pre, Post) rmANOVA. One-sample t-tests were used to determine whether the change in cMEP amplitude was significant. rmsEMG and time to EMG onset were tested with a 2 TASK (Flexion, Pronation) × 2 STIMULATION (cTBS, Sham cTBS) × 2 SIDE (Right, Left) × 2 TIME (Pre, Post) rmANOVA.

BB iMEPs and rmsEMG. Responses in left BB evoked by TMS of left M1 at 80% MSO were rectified and then averaged and inspected for iMEPs between 15 and 45 ms after stimulus (Chen et al. 2003; Lewis and Perreault 2007). When iMEPs were present, the onset and offset latencies for the largest iMEP for that participant were used to calculate iMEPAREA (18- to 40-ms window depending on the individual). A window of background EMGAREA equivalent to that of the iMEPAREA analysis window for the same trial was used to calculate prestimulus EMGAREA. To provide a measure of iMEP size, prestimulus EMGAREA was subtracted from the iMEPAREA using the following formula

\[ \text{iMEP} = (\text{iMEP}\text{AREA} - \text{EMG}\text{AREA}) \times 1,000 \]

where iMEPAREA and EMGAREA were converted to mV·s. The change in left BB iMEPAREA after cTBS was expressed as a percentage of pre-cTBS BB iMEPAREA, as for cMEP amplitude. A one-sample t-test was used to test the difference from baseline, whereas a paired t-test was used to determine whether the change in BB iMEPAREA differed between cTBS and sham cTBS.

The latency of the left BB iMEP was determined in the same EMG traces, because the first deflection from baseline in each trace of rectified EMG, and averaged. Prestimulus rmsEMG was calculated from the same traces as iMEPs. Left iMEP latency and rmsEMG

<table>
<thead>
<tr>
<th>Task</th>
<th>Statistical Test</th>
<th>N</th>
<th>Effect and P Value</th>
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<tbody>
<tr>
<td>BB ER</td>
<td>Flexion, pronation</td>
<td>2 STIMULATION × 2 SIDE × 2 TIME</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TIME × STIMULATION P = 0.006</td>
</tr>
<tr>
<td>BB cMEP amplitude</td>
<td>Flexion, pronation</td>
<td>2 TASK × 2 STIMULATION × 2 SIDE</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>SIDE P = 0.04</td>
</tr>
<tr>
<td>BB cMEP latency</td>
<td>Flexion</td>
<td>2 STIMULATION × 2 SIDE × 2 TIME</td>
<td>9</td>
</tr>
<tr>
<td>Time to EMG onset</td>
<td>Flexion, pronation</td>
<td>2 TASK × 2 STIMULATION × 2 SIDE × 2 TIME</td>
<td>9</td>
</tr>
<tr>
<td>Right BB sICI</td>
<td>Rest</td>
<td>3 STIMULATION × 3 INTENSITY × 2 TIME</td>
<td>9</td>
</tr>
<tr>
<td>BB iMEP latency</td>
<td>Flexion</td>
<td>2 STIMULATION × 2 TIME</td>
<td>5</td>
</tr>
<tr>
<td>BB iMEP area</td>
<td>Flexion</td>
<td>2 STIMULATION × 1 TIME</td>
<td>5</td>
</tr>
<tr>
<td>BB iSPs</td>
<td>Flexion</td>
<td>2 STIMULATION × 2 TIME</td>
<td>7</td>
</tr>
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</table>

BB, biceps bradii; ER, excitability ratio; cMEP, contralateral motor-evoked potential; iMEP, ipsilateral motor-evoked potential; iSP, ipsilateral silent periods.
were analyzed using a 2 STIMULATION (cTBS, Sham cTBS) × 2 TIME (Pre, Post) rmANOVA.

IPSILATERAL SILENT PERIOD. Ipsilateral silent periods (iSPs) were evoked in left BB with single-pulse TMS (80% MSO) delivered to left M1. From the rectified, averaged traces, SP onset was defined as the time when the poststimulus EMG fell continuously (for ≥10 ms) below the mean of the prestimulus EMG, in a window 30–60 ms after the stimulus, and ended at the first time when EMG returned to baseline (Avanzino et al. 2007; Chen et al. 2003; Trompetto et al. 2004). The area between onset and offset below the mean of the prestimulus rmsEMG was calculated. In participants with iSPs, left BB iSPAREA and rmsEMG from the same averaged traces were analyzed separately using a 2 STIMULATION (cTBS, Sham cTBS) × 2 TIME (Pre, Post) rmANOVA.

SICI. SICI in left M1 was calculated at each conditioning stimulus intensity, as the percent inhibition of the nonconditioned MEP amplitude using the following formula

\[ \text{SICI} = 100 \times \left( \frac{C - \text{NC}}{C} \times 100 \right) \]

where C and NC correspond to average conditioned and nonconditioned BB MEP amplitude, respectively. Higher values represent increased SICI, and smaller values represent decreased SICI. Only nonconditioned cMEPs with amplitude >0.1 mV were accepted for analysis. The two sessions of cTBS were compared with the single session of sham cTBS using a 3 STIMULATION (Right cTBS, Left cTBS, Sham cTBS) × 3 INTENSITY (70, 85, 100% AMT) × 2 TIME (Pre, Post) rmANOVA. To ensure right BB was at rest during paired-pulse TMS, rmsEMG was calculated 100 to 1 ms before the stimulus in the same averaged traces and analyzed as for BB cMEPs. Significance level was set at \( P < 0.05 \). rmANOVAs were tested for nonphericity and corrected where necessary. Post hoc t-tests were used to explore significant main effects and interactions and were corrected for multiple comparisons (Rom 1990).

RESULTS

No participants experienced any adverse events from the procedures. A summary of results is presented in Table 2. Trace figures from a representative participant showing left BB cMEPs and iMEPs before and after cTBS can be seen in Fig. 1.

BB contralateral MEPs

ERs increased in the right and left BB after cTBS of left M1 (Fig. 2). There was a main effect of TIME (\( F_{1,8} = 19.01, P < 0.01 \)) and a TIME × STIMULATION interaction (\( F_{1,8} = 13.75, P < 0.01 \)), with no effect or interaction with SIDE. Paired t-test showed that, in the real cTBS sessions, the right BB ER increased from 0.23 to 0.30 (\( P = 0.001 \)), and the left BB ER increased from 0.22 to 0.33 (\( P = 0.002 \)). Sham cTBS had no effect on ERs (both \( P > 0.60 \)). There were no other main effects or interactions for ER (all \( P > 0.33 \)).

Right BB cMEPs were suppressed before flexion, and left BB cMEPs were facilitated prior to pronation after cTBS (Fig. 3). For BB cMEP amplitude, there was a main effect of SIDE (\( F_{1,8} = 11.36, P = 0.01 \)) and TASK (\( F_{1,8} = 5.67, P < 0.05 \)), and a TASK × STIMULATION interaction (\( F_{1,8} = 7.52, P < 0.05 \)). The TASK × STIMULATION × SIDE interaction was not significant (\( P = 0.06 \)). Before flexion, right BB cMEPs were suppressed relative to sham for right BB (cTBS −31 ± 21%, sham cTBS −5 ± 21%, \( P = 0.036 \)) and left BB cMEPs were unaffected (cTBS −10 ± 17%, sham cTBS 5 ± 29%, \( P > 0.36 \); Fig. 1A). Before pronation, left BB cMEPs were facilitated relative to sham (cTBS 31 ± 24%, sham cTBS −6 ± 19%, \( P = 0.007 \); Fig. 1B) and unchanged for right BB (cTBS −18 ± 29%, sham cTBS −4 ± 22%, \( P > 0.31 \)). One-sample t-tests found right BB cMEP suppression (before flexion; \( P =
main effect of TIME (findings of interest in the prestimulus rmsEMG. There was a before and after the intervention, respectively. There were no 0.045) in the RightcTBS session, but this was not significant AMT, SICI increased from 45.4 6.7%, post 41.5 8.4 ms; postintervention, 129 18% mV). This difference in rmsEMG over time would not have affected the BB cMEP responses to cTBS, because the values show BB was at rest at the time of stimulation. There were no main effects or interactions for the time to EMG onset: preintervention, 126.5 8.4 ms; postintervention, 129 7.9 ms (all P > 0.09).

To assess left M1 SICI, cMEPs were recorded in right BB at rest. SICI increased in both cTBS sessions. There was no change in left M1 SICI after sham cTBS (Fig. 4). There was a main effect of INTENSITY on SICI (F(2,7) = 13.35, P = 0.001), an INTENSITY TIME interaction (F(2,7) = 4.77, P < 0.05), and a STIMULATION TIME interaction (F(2,7) = 6.54, P < 0.05). There were no other main effects or interactions (all P > 0.08). With CS intensity of 70% AMT, SICI increased in both the RightcTBS session (pre 25.8 ± 5.9%, post 43.8 ± 1.8%, P = 0.006) and the LeftcTBS session (pre 28.2 ± 6.7%, post 41.5 ± 7.1%, P = 0.08). With CS intensity of 85% AMT, SICI increased from 45.4 ± 7.1 to 58.4 ± 6.8% (P = 0.045) in the RightcTBS session, but this was not significant when adjusted for multiple comparisons. There were no effects at other intensities or after sham cTBS (all P > 0.12).

There were no main effects or interactions for prestimulus rmsEMG (all P > 0.18). rmsEMG was consistently at rest (preintervention: 0.004 ± 0.001 mV; postintervention, 0.004 ± 0.002 mV).

**BB iMEPs and iSPs**

Left BB iMEPs were facilitated after cTBS (Fig. 1C), with changes in both amplitude and latency (Fig. 5). Ipsilateral iMEPs were observed in five of nine participants. One-sample t-tests showed facilitation of iMEPAREA after cTBS compared with baseline (79 ± 8%, P = 0.035). Paired tests found iMEP facilitation after cTBS was significant compared with sham cTBS (cTBS 79 ± 8%, sham cTBS −18 ± 4%, P = 0.017). There was a STIMULATION TIME interaction for left BB iMEP latency (F(1,4) = 12.52, P < 0.05). Mean latency pre-cTBS was 24.4 ± 1.5 ms, decreasing to 22.1 ± 1.6 ms after cTBS (P = 0.001). Latency was not altered by sham cTBS (pre 23.8 ± 1.6 ms, post 24.4 ± 1.8 ms, P = 0.27). There were no effects or interactions for rmsEMG (all P > 0.24). Average rmsEMG values were 0.013 ± 0.003 mV before intervention and 0.014 ± 0.005 mV after intervention.

iSPs occurred in seven of nine participants and were unaffected by cTBS. There were no main effects or interactions for iSPAREA in left BB (all P > 0.47). There were no main effects or interactions for rmsEMG (all P > 0.08). Average rmsEMG values were 0.016 ± 0.005 mV before intervention and 0.015 ± 0.004 mV after intervention.

**FIG. 2.** Excitability ratio (ER) calculated from MEPs in the left and right BB before and after cTBS (●) and sham conditions (○). Each point is the group average (n = 9). There was a TIME STIMULATION interaction (†P < 0.01). The ER increased bilaterally after real but not sham cTBS. Error bars indicate SE.

**FIG. 3.** Average BB cMEP amplitude after cTBS (black) and sham cTBS (gray), normalized to baseline (n = 9). There was a TASK STIMULATION interaction. A: in the flexion task, right BB cMEPs were suppressed after cTBS compared with sham cTBS (†P < 0.05) and baseline (†P < 0.01). Error bars indicate SE. B: in the pronation task, left BB cMEPs were facilitated compared with sham cTBS and baseline (†P < 0.01). Error bars indicate SE.
This study provided a novel demonstration that cTBS of left M1 can degrade selective muscle activation in both contralateral and ipsilateral arms. This finding builds on the idea that both contralateral and ipsilateral M1 are involved in upper limb control (Perez and Cohen 2008) and extends our understanding specifically for the control of proximal muscles. Left hemisphere cTBS altered selective muscle activation in both arms, but there was a dissociation of effect between the two sides. The first novel finding was that in the ipsilateral left arm, the ER increased because of facilitation of left BB cMEPs before pronation, analogous to that observed in chronic stroke patients (Gerachshenko et al. 2008). The second novel finding was that the ER increased in the contralateral right arm after cTBS, because of a dampening of premovement facilitation in right BB before flexion. These results indicate cTBS suppressed contralateral facilitatory output to right BB and ipsilateral inhibitory output to left BB. The potential mechanisms underlying this effect are discussed in the following text. The third novel finding was that cTBS facilitated iMEPs from left M1 to left BB, which has never been shown to our knowledge. This may indicate that cTBS reduced descending inhibition over ipsilateral BB αMNs. This may have, in part, contributed to the loss of selective inhibition that facilitated left BB cMEPs during pronation in the left arm.

Selective muscle activation in ipsilateral arm

Few studies have examined changes in the ipsilateral arm after M1 cTBS, and these have only been done so by recording hand muscle cMEPs evoked from the hemisphere contralateral to TBS delivery (Iezzi et al. 2010; Ishikawa et al. 2007; Stefan et al. 2008; Suppa et al. 2008). Together, they provide no consistent evidence of either facilitatory or suppressive effects on cMEPs evoked from the unstimulated M1. This study was the first to examine the effects of cTBS on proximal muscles of the ipsilateral upper limb. Left BB cMEPs were facilitated before pronation but not before flexion. This is a novel demonstration of an effect of cTBS on selective activation of the ipsilateral BB muscle. This confirms that ipsilateral M1 (together with contralateral M1) is important for motor control of the proximal upper limb, given that ipsilateral projections are densely distributed to proximal αMNs (Kuypers 1964). Although the pathways mediating the effects on left BB cMEPs are difficult to discern precisely, they may include inhibitory ipsilateral projections from left M1 exerting an effect at the level of the αMNs. Although contralateral M1 is responsible for the facilitation of agonist and suppression of antagonist αMNs before a muscle contraction (Gerachshenko and Stinear 2007; Hoshiyama et al. 1996), projections from ipsilateral M1 provide a pathway for additional inputs to αMNs. Anatomical studies in the cat and nonhuman primate indicate descending projections from ipsilateral M1 terminate on interneurons mediating inhibition of agonist and antagonist αMNs in the spinal cord (Alstermark et al. 1984, 2007; Illert and Tanaka 1978; Illert et al. 1977, 1981; Isa et al. 2006). In this study, down-regulation of ipsilateral tonic inhibition after cTBS of left M1...
Selective muscle activation in contralateral arm

transcallosal inhibition.

Therefore the effect on selective muscle activation

M1 would be expected to facilitate left BB cMEPs before

resulted from reduced transcallosal inhibition (TCI) from

studies of ipsilateral M1 contribution to selective activation

factor in the increase of left BB cMEPs before pronation.

Another candidate mechanism involves PNs located at the

projecting to shoulder abductors and elbow flexors (Davidson

PNs) in the cervical spinal cord. It is unlikely that the effects

cTBS were primarily mediated by reduced inhibition of the

PNs project to spinal αMNs with a somatotopic organization that facilitates synergistic recruitment of specific distal and proximal muscles (Gracies et al. 1991; Nicolas et al. 2001). In humans, PNs are held under tonic inhibitory control, which is selectively released during volitional movement when particular muscles are required for the task (Iglesias et al. 2007; Nicolas et al. 2001; Roberts et al. 2008). An expected outcome of decreased inhibition of BB PNs would be inappropriate facilitation of BB cMEPs before pronation. In contrast, inhibition of BB PNs would normally be released before elbow flexion, so the downregulation of PN inhibition by cTBS would have no further effect on BB cMEPs in this task. This particular mechanism did not inform our a priori hypothesis and was not studied here. However, it warrants further examination in future studies of ipsilateral M1 contribution to selective activation in proximal upper limb muscles.

It is unlikely that our findings in the left arm after cTBS resulted from reduced transcallosal inhibition (TCI) from left to right M1. In this study, TCI was estimated by the indirect measure of iSP (Trompetto et al. 2004). iSP was unchanged in left BB after cTBS, in line with other studies (Stefan et al. 2008; Suppa et al. 2008). Disinhibition of right M1 would be expected to facilitate left BB cMEPs before both pronation and flexion, but only the former was observed. Therefore the effect on selective muscle activation in the left arm is not readily explained by a reduction in transcallosal inhibition.

Selective muscle activation in contralateral arm

The ER of the right arm was increased after cTBS, as BB cMEPs were reduced before flexion, and unchanged before pronation. Continuous TBS is known to suppress excitability of corticospinal projections to contralateral αMNs (Gentner et al. 2008; Huang et al. 2005; Ishikawa et al. 2007; Stefan et al. 2008; Suppa et al. 2008). After cTBS, BB cMEPs were less facilitated before activation as an agonist to elbow flexion. cTBS increased SICI in left M1, thereby reducing corticomotor excitability and selective activation of the agonist BB (Byblow and Stinear 2006; Stinear and Byblow 2003). There was no further suppression evident before pronation because BB cMEPs were strongly suppressed in this task, i.e., before and after cTBS.

Limitations of this study

Our task dictated that BB cMEPs were evoked just before the onset of muscle contraction. It is not possible to examine iMEPs and iSPs within the same task given that a stable isometric muscle contraction is required to elicit these responses. Similarly, SICI was assessed in left M1 with right BB at rest using a salient inhibition recruitment curve technique to examine left M1 intracortical changes after cTBS. Assessment of SICI would be fraught if performed concurrently during the motor task given that SICI would be released during premovement facilitation and unable to reflect possible changes induced by TBS. It is possible that future studies might be able to examine SICI bilaterally during this task, but the challenges might preclude analysis of other variables of potentially greater interest. The main novel contribution of this study relates to the fact that cTBS altered the excitability ratio and iMEPs of the ipsilateral arm in particular. However, it cannot be overlooked that all measures were not obtained under the same task conditions, and the potential confounds introduced by this cannot be known.

Clinical implications

Continuous TBS of left M1 degraded selective activation of BB in the ipsilateral arm of healthy participants. The ER increased because left BB cMEPs before pronation were facilitated, similar to those observed in chronic stroke patients (Gerachshenko et al. 2008). In the experiment of Gerachshenko et al. (2008), ERs correlated negatively with Fugl-Meyer upper limb scores highlighting the potential utility of ER as a neurophysiological correlate of abnormal upper synergy after stroke. The results of this study in healthy humans indicate a role for ipsilateral M1 in abnormal synergy formation consistent with current ideas that the origin of abnormal muscle synergies after stroke is the contralesional hemisphere (Schwerin et al. 2008; Yao et al. 2009). Although stroke is a chronic condition and effects on M1 evoked by cTBS in this study were acute, our results may provide additional evidence that contralesional M1 contributes to abnormal muscle synergies in the paretic upper limb.

The prevalent model of motor cortex physiology after stroke is one of interhemispheric competition whereby the ipsilesional M1 becomes underexcitable and the contralesional M1 becomes hyperexcitable (Murase et al. 2004; Traversa et al. 1998). Noninvasive stimulation protocols have been used in an attempt to redress this imbalance of hemispheric excitability (Hummel and Cohen 2006). For example, cTBS of contralesional M1 has been used to try to suppress its excitability and improve paretic hand function. To date, outcomes have been
mixed (Ackerley et al. 2010; Bolognini et al. 2009; Di Lazzaro et al. 2008; Nowak et al. 2009; Talelli et al. 2007). It is worth keeping in mind that cTBS applied to the contralesional M1 after stroke may have unintended deleterious consequences for control of proximal muscles of the paretic limb. Further studies with patients are warranted to investigate the effects of noninvasive stimulation protocols on selective muscle activation and synergy formation in the paretic upper limb.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

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