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Interhemispheric enhancement of somatosensory cortical excitability through contralateral repetitive transcranial magnetic stimulation

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ABSTRACT

Objectives: Somatosensory evoked potentials (SEPs) were used to index somatosensory–somatosensory interhemispheric interactions and highlight potential mechanisms by which TMS alters contralateral somatosensory cortex excitability.
Methods: Fifteen healthy individuals participated in three sessions on separate days. On each day participants received either: (1) continuous theta burst (cTBS), (2) 1 Hz repetitive transcranial magnetic stimulation (rTMS) or (3) control TMS over left somatosensory cortex. SEPs from right somatosensory cortex were recorded before and after TMS while participants were at rest, performed sensorimotor tracking or the sustained attention to response task (SART). Left-handed tracking performance was also indexed.
Results: N20–P27 amplitude was increased following 1 Hz rTMS while participants were at rest. This increased amplitude was not observed during right-handed tracking or the SART. N20–P27 amplitude was not influenced by cTBS or control TMS. P15–N20 and N34–P50 SEP components were not influenced by TMS. Right- and left-handed tracking performance was not transiently influenced by TMS.
Conclusions: The results support TMS induced somatosensory–somatosensory interactions and offer converging evidence for an intercortical, rather that intracortical, mechanism that mediates contralateral sensory processing. These interactions appear to be dependent on concurrent attention/task demands.
Significance: Somatosensory–somatosensory interactions are reflected by intercortical mechanisms that are state and task dependent.

1. Introduction

Extensive research has demonstrated interhemispheric interactions between the ipsilateral and contralateral motor cortices (Kobayashi et al., 2009; Murase et al., 2004; Duque et al., 2005; Butefisch et al., 2008; Perez and Cohen, 2008). In addition to these interactions, stimulation of the motor cortex has been shown to influence sensory thresholds and cortical excitability of contralateral somatosensory cortex (Seyal et al., 2005; Ishikawa et al., 2007; Uguisu et al., 2010). However, evidence for somatosensory–somatosensory interactions is relatively ambiguous and not been investigated during sensorimotor control.

Recently the potential relevance of somatosensory–somatosensory interactions have been highlighted in the stroke-affected brain. After stroke, altered interhemispheric interactions between both the ipsilateral and contralateral motor cortices, as well as the ipsilateral and contralateral somatosensory cortices, contribute to motor deficits (Calautti et al., 2007). Further, reducing sensory afference through acute peripheral deafferentation, using a topical anesthetic or ischemic nerve block, results in increased functional ability of the contralateral limb (Werhahn et al., 2002b; Floel et al., 2004, 2008; O'Bryant et al., 2007; Voller et al., 2006). These changes in behavior have been linked to shifts in somatosensory cortical excitability ipsilateral to the non-deafferented hand (Werhahn et al., 2002b) as well as to altered ipsilesional motor cortical excitability (Werhahn et al., 2002a).

There are numerous observations of interhemispheric interactions between the somatosensory cortices suggesting the presence of interhemispheric somatosensory influences (Staines et al., 2002b; Hlushchuk and Hari, 2006; Seyal et al., 1995; Blankenburg et al., 2008; Meehan et al., 2008; Clarey et al., 1996). However, studies using transcranial magnetic stimulation (TMS) have produced variable results (Ishikawa et al., 2007; Seyal et al., 1995;

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Blankenburg et al., 2008; Meehan et al., 2008; Ragert et al., 2004, 2008; Tegenthoff et al., 2005).

Behavioral and functional magnetic resonance imaging (fMRI) studies demonstrate altered tactile perception (Seyal et al., 1995) or altered blood oxygen level dependent response (Blankenburg et al., 2008) with concurrent application of TMS over the sensory cortex of the contralateral hemisphere. However, studies using somatosensory evoked potentials prior to and immediately after application of repetitive TMS (rTMS) over contralateral sensory suggest that the effects of stimulation do not last after its cessation, despite persistent changes in the cortex immediately underneath the stimulation site (Ishikawa et al., 2007; Ragert et al., 2004, 2008; Tegenthoff et al., 2005).

There are two possible explanations for the variability in the findings of TMS studies of somatosensory–somatosensory interactions: the use of different dependent measures, and/or the failure to control for the potential effects of arousal and attention on cortical excitability. Further, these explanations are not mutually exclusive.

A number of SEP studies have used paired-median nerve stimulation before and after application of TMS over somatosensory cortex (Ragert et al., 2004, 2008; Tegenthoff et al., 2005). Though this approach is sensitive to intracortical changes, it is possible that intercortical mechanisms supporting peripheral–central sensory relays (Staines et al., 2002a) has an equal influence on the amplitude of both the baseline potential and subsequent potential. Equivalent changes between the baseline and subsequent potentials would cause paired-median nerve stimulation to be insensitive to intercortical somatosensory–somatosensory interactions.

With respect to the effects of arousal and/or attention on somatosensory–somatosensory interactions, the limited work using single median nerve stimulation to index somatosensory–somatosensory effects required that participants lay supine with their eyes closed. Plasticity is sensitive to the locus of attention (Stefan et al., 2004) and TMS induced effects are state (Blankenburg et al., 2008) or task dependent (Meehan et al., 2008). Thus, it is possible that any somatosensory interactions were weakened by reductions in arousal and/or attention that resulted from the experimental set-up.

Therefore, the purpose of the current study was to investigate the presence of TMS induced interhemispheric interactions using somatosensory evoked potentials. We assessed SEP amplitude before and after three different types of TMS delivered on three separate days: (1) 1 Hz rTMS, (2) continuous theta burst stimulation (cTBS) and (3) control TMS.

To account for the possibility that somatosensory–somatosensory interactions are not mediated by intracortical mechanisms, SEPs were elicited by single left median nerve stimulation before and after TMS on each day. To control for the effects of arousal/attention we required participants to actively fixate a central target during rest. Further, SEPs were also recorded while participants performed a right-handed tracking task or a general attentional control task (the sustained attention to response task; SART).

It was hypothesized that, if somatosensory–somatosensory interactions were mediated by intercortical mechanisms associated with sensory relay, SEP components reflecting early sensory processing (N20–P27 SEP component) would be increased after 1 Hz rTMS and cTBS but not control TMS. Further, we predicted that somatosensory–somatosensory mechanisms may interact with task demands such that having to sustain attention to the right-hand to monitor sensory re-afference during tracking would result in greater somatosensory "gating" of afference/re-afference from the contralateral limb to S1 and negate any increases in SEP amplitude after application of 1 Hz rTMS and cTBS (Meehan et al., 2008, 2009). The SART was used to index the effect of sustained attention in general.

Secondarily, we hypothesized that TMS induced plasticity would acutely disrupt contralateral right-handed tracking and benefit left-handed tracking. To account for this possibility, participants completed trials with their left and right hands.

2. Methods

2.1. Participants

Fifteen healthy volunteers (6 male, 9 female, average age 26.4 years, SD = 7.9 years) were recruited. All participants gave their informed consent to participate in the study and the Office of Research Ethics at the University of British Columbia approved the experimental procedures.

2.2. Experimental design

The study consisted of three sessions run on separate days. During each session participants completed four experimental conditions before and after application of one of the three TMS interventions: cTBS, 1 Hz rTMS or sham control rTMS. The four testing conditions consisted of rest, left-handed continuous sensorimotor tracking, right-handed continuous sensorimotor tracking, and the SART. To assess changes in cortical excitability, SEPs elicited from the single left median nerve (MN) stimuli were recorded during rest, right-handed tracking and the SART task. SEPs were not recorded during left-handed tracking so as not to interfere with tracking performance.

The order of stimulation and task performance was counterbalanced across days.

2.3. Tasks

2.3.1. Rest

Participants were seated in front of a computer monitor with both arms resting and secured in concave armrests. During the acquisition of SEPs participants were required to maintain fixation to a target placed in the center of the computer screen. The duration of the rest condition was approximately 3 min and was equivalent to the time to complete the sensorimotor tracking and SART conditions. This ensured that equal numbers of MN stimuli were delivered in each condition.

2.3.2. Tracking

Continuous sensorimotor tracking was performed unilaterally by either the right (RH Tracking) or left (LH Tracking) hands. Participants were seated in front of a computer monitor with both arms resting securely in concave arm rests with the relevant hand holding one of two vertical handle bars placed in line with the arms of the chair. Participants were instructed to relax the hand not being used during the tracking task. The sensorimotor task consisted of an open white circle and a red dot that moved vertically down the center of the screen at a constant rate of 44 pixels per second. The red dot was defined as the tracking target and its horizontal position randomly fluctuated left and right around the vertical axis.

Participants used the vertical handle bar to control the horizontal position of the white circle and were instructed to keep the red dot in the center of their white circle. Wrist position sampling and all stimuli presentation occurred at 40 Hz using custom software developed on the LabView platform (v. 8.6; National Instruments Co., Austin, TX). To maximize reliance upon somatosensory information, the hand that controlled the cursor was occluded from view and no tail was left on the screen to indicate trajectory. Finally, the white cursor controlled by the participant was only visible for 200 ms of every 2 s of tracking to minimize feedback about

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position. This ratio was chosen as it has been shown to be below the critical frequency at which visual feedback can be used to directly guide motor response (Kao, 1976).

The pattern of target movement was predefined according to a method modified from Wulf and Schmidt (1997). A unique 16-s trial was constructed from one 1 s baseline and three 5 s sine–cosine segments. Participants performed 16 blocks of tracking lasting approximately 262 s. Segments were constructed from random sets of coefficients using the polynomial equation as described by Wulf and Schmidt (1997), modified to include additional controls on waveform velocity (Vidoni and Boyd, 2008). Different waveforms were used pre- and post-stimulation, and across each testing day; however, the same waveforms were used for each participant. Root mean square error (RMSE) indexed motor performance and was defined as the average of the difference between target location and the participant controlled cursor position across all trials. To further investigate the changes associated with application of TMS we decomposed RMSE into spatial error and time-lag components (Boyd and Winstein, 2004).

2.3.3. Sustained attention to response task (SART)

Participants were seated in the same position as at rest; however, during fixation they were presented with a single digit number ranging from 1 to 9. One block of 200 trials was performed. Participants were instructed to respond as fast and accurately as possible when a digit appeared on the screen to depress the space bar on a keyboard with the right hand. A response triggered the presentation of the next digit following an inter-trial interval that was pseudo-randomly varied in length (square wave distribution, 750–1500 ms). Participants were instructed not to respond if the digit that appeared was a 3. If the participants correctly inhibited their response when the 3 appeared it remained on screen for 2000 ms before the next trial was initiated. If the participants incorrectly responded to the digit 3 the next trial was initiated as if the digit had been any other. The probability of a 3 appearing on any given trials was 0.11. Including response times, a block of 200 trials lasted approximately as long as the sensorimotor tracking task and the rest condition.

Responses to digits 1, 2, 4, 5, 6, 7, 8, 9 between 250 and 2000 ms following the appearance of the number or correct non-response to the digit 3 between 0 and 2000 ms were categorized as hits; responses to digits 1, 2, 4, 5, 6, 7, 8, 9 between 0 and 250 ms following the appearance of the number or any response to the digit 3 were categorized as false alarms. Failure to respond to digits 1, 2, 4, 5, 6, 7, 8, 9 between 250 and 2000 ms following the appearance of the number were categorized as misses. Response time (RT) was calculated from hits in response to the digits 1, 2, 4, 5, 6, 7, 8 and 9. Errors were calculated as a percentage of the total number of 3s presented in the block. False alarms and misses were not analyzed due to their relative paucity.

2.4. Transcranial magnetic stimulation

TMS was delivered with a Magstim Super Rapid^2 stimulator using a 70 mm figure-8 air-cooled coil (Magstim Company Ltd., Wales, UK). Participants were seated in a semi-reclined dental chair with their arms bent and supported by armrests. The TMS coil was oriented tangentially to the scalp with the handle at 45° to the midline in a posterior lateral orientation. Prior to the experiment, high-resolution anatomical magnetic resonance images (MRI) were acquired for each participant (TR = 12.4 ms, TE = 5.4 ms, flip angle $\theta = 35°$, FOV = 256 mm, 170 slices, 1 mm thickness) at the UBC MRI Research Centre on a Philips Achieva 3.0 T whole body MRI scanner (Phillips Healthcare, Andover, MD) using a sensitivity encoding head coil (SENSE). These images were then imported into the BrainSight™ TMS neuronavigation software (BrainSight 2.0, Rogue Research Inc., Montreal, QC) to allow for stereotaxic registration of the TMS coil with the participants' anatomy for online control of coil positioning during each session and across days.

Surface electromyography (EMG) over the participants right flexor carpi radialis (FCR) was monitored using the evoked potential unit of the Super Rapid^2 control unit (Magstim Super Rapid^2, Magstim Company Ltd.). Initially, the FCR representation was marked on the participants anatomical MRI as the medial edge of the left "hand knob". This point acted as a starting point for determination of the motor "hot spot" for FCR. Motor evoked potentials were then used to determine the coil position that evoked the maximal response in the right FCR. The location and trajectory of the coil over left primary motor cortex (M1) were then marked using the BrainSight™ stereotaxic software to minimize variability within and across days. Resting motor threshold (RMT) was determined for each participant as the percentage of stimulator output that elicited an MEP of $\geqslant$50 μV peak to peak on 5 out of 10 trials. After determination of RMT, active motor threshold (AMT) was determined as the percentage of stimulator output that elicited an MEP of $\geqslant$200 μV peak to peak on 5 out of 10 trials while participants maintained a contraction of the FCR at 20% of their maximal force. Force was monitored using a custom pressure system with a gauge upon which the target force was marked.

The site of stimulation for the left primary somatosensory cortex was initially marked on the anatomical MRI using BrainSight™. Left S1 was placed posterior to the central sulcus 2 cm posterior and 1 cm lateral to the FCR "hot spot" (Vidoni et al., 2010). Isolation of this area from M1 was verified using single-pulses to ensure that there was no muscle activity as recorded using EMG over the FCR and visual inspection of the arm. Once confirmed the location and trajectory of the coil was recorded using BrainSight™ to ensure the same location was stimulated on each day. cTBS stimulation was delivered at 80% AMT and consisted of three pulses presented at 50 Hz repeated every 200 ms for a total of 40 s (Huang et al., 2005). 1 Hz rTMS was delivered at 90% of RMT and consisted of 1200 pulses presented in trains of 10 pulses with a 1 s interval between the trains for a total of 20 min. Control TMS was delivered using a custom coil that mimicked appearance and sound of either the cTBS or 1 Hz rTMS but did not induce any current in the underlying cortex (Magstim Company Ltd.). The type of control stimulation cTBS or 1 Hz rTMS was counterbalanced across participants. Due to the difference in length and sound of the different stimulation protocols participants were aware of differences across the sessions; however, all participants were naïve to the anticipated effects of the stimulation during any given session.

2.5. Recording and quantification of evoked potentials

SEPs were elicited during rest, RH Tracking and the SART task. SEPs were derived from electrical stimulation to the MN at the wrist of the left hand. Square wave pulses of 0.5 ms duration (GRASS SD9 Stimulator with SIU-V Isolation Unit, West Warwick, RI) were delivered through surface electrodes fixed to the wrist. MN stimuli were delivered with an ISI of 0.8 s for a total of 210 stimulations per condition.

MN stimulus intensity was set to motor threshold. To ensure changes in MN stimulus intensity did not account for changes in SEP amplitude, the amplitude of the evoked M-wave was recorded via surface electromyography (EMG) electrodes placed over the thenar eminence supplied by the MN. M-wave amplitude was monitored and maintained in real time to ensure consistent stimulation of the MN within and across collection days. Consistency of stimulus intensity was also verified during off-line analysis. EMG recordings were amplified (2000×) and bandpass filtered (1–200 Hz) (Grass Neurodata 12 EEG Amplification System) before

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being digitized (1000 Hz, using custom software, LabView 8.6, PCI-6078E Series A/D board with a SCB-99 pin-out), and stored for later analysis.

Electroencephalographic (EEG) data were recorded from the Fz, Cz, Pz, C4, Cp4 and P4 electrode sites (32 channel Electro-Cap, Electro-Cap International Inc., Eaton, OH) in accordance with the international 10–20 system for electrode placement, and referenced to the mastoid. All channel recordings had impedance of 5 kΩ or less. Eye movements were recorded by electrooculogram (EOG). EEG and EOG data were amplified (20,000×), filtered (1–200 Hz, 6 dB octave roll-off, Grass Neurodata 12 EEG Amplification System) and digitized (1000 Hz, using custom software, LabView 8.6, PCI-6078E Series A/D board with a SCB-99 pin-out) before being stored for off-line analysis. EEG containing ocular and/or movement artifact was excluded from further analysis.

SEPs were extracted using the EEGLab toolbox (Institute for Neural Computation, University of California – San Diego, San Diego, CA) for MATLAB v2009 (The MathWorks, Natick, MA) environment. SEPs were extracted by averaging together baseline corrected epochs time locked to MN stimulation (within −50 to 200 ms). SEPs were filtered using a bandpass filter (2–175 Hz). Approximately 180 artifact free MN stimuli were then used to derive the SEPs for each participant and condition.

2.6. SEP data analyses

For all conditions the peak-to-peak amplitudes of the P15–N20, N20–P27 and N34–P50 parietal SEP components were measured for each subject from electrode site Cp4. This site was chosen based upon topographic inspection of the morphology of the SEP traces in all six channels and ablation studies localizing the N20 and P27 SEP components to Brodmann Areas 3b and 1 of the primary somatosensory cortex (Allison et al., 1991; Desmedt and Tomberg, 1989). Latencies of the P15, N20, P27, N34 and P50 SEP components were measured from the MN stimulus onset to the peak of the SEP component. P15–N20 amplitude was defined as the change in amplitude from the negative peak at approximately 20 ms post MN stimulus to the preceding positive peak. The N20–P27 amplitude was defined as the change in amplitude from the negative peak at approximately 20 ms to the subsequent positive peak. N34–P50 amplitude was measured as the change in amplitude from positive peak between 45 and 55 ms post MN stimulus to the preceding negative peak.

Changes in SEP amplitude pre- and post-cTBS, 1 Hz rTMS and control rTMS were investigated using separate 2 (Time: Pre-TMS, Post-TMS) × 3 (TMS Session: cTBS, 1 Hz rTMS and Control rTMS) repeated measures ANOVAs for each condition (Rest, RH Tracking, SART). Greenhouse–Geisser epsilon corrections were employed where applicable. Significant results were investigated using hypothesis-guided contrasts, corrected for multiple comparisons using the modified Bonferroni method, where applicable.

M-wave amplitudes were quantified (peak-to-peak) from EMG electrodes placed over the thenar musculature of the hand receiving MN stimulation and analyzed using similar ANOVAs as detailed above. This analysis ensured that MN stimulation did not vary or contribute to SEP differences observed.

2.7. Behavioral data analyses

Sensorimotor tracking performance was assessed for changes in overall RMSE, spatial error RMSE and lag using separate 2 (Hand: Left, Right) × 2 (Time: Pre-TMS, Post-TMS) repeated measures ANOVAs for each TMS Session (cTBS, 1 Hz rTMS, control TMS).

Reaction times and errors during the SART task pre and post each TMS variant were analyzed using separate 2 (Time: Pre-TMS, Post-TMS) × 3 (TMS Session: cTBS, 1 Hz rTMS, control TMS) ANOVAs.

For all behavioral analyses Greenhouse–Geisser epsilon corrections were employed and significant results were investigated using hypothesis-guided contrasts, corrected for multiple comparisons using the modified Bonferroni method, where applicable.

3. Results

3.1. SEP amplitude

The grand average waveforms elicited pre and post each variant of TMS during Rest, RH Tracking and the SART task at electrode Cp4 are shown in Fig. 1. The mean peak-to-peak amplitudes of the N20–P27 SEP component at Cp4 are shown in Fig. 2. The mean amplitude of the P15–N20, N20–P27 and N34–P50 SEP components are shown in Table 1.

The two-way repeated measure ANOVA on N20–P27 amplitude during rest revealed a significant TMS Session × Time interaction [$F(2, 28) = 3.58$, $\varepsilon = 0.83$, $p < 0.05$], as well as main effect of Time [$F(1, 14) = 4.72$, $p < 0.05$]. The significant interaction can be attributed to a significant increase in N20–P27 amplitude after application of 1 Hz rTMS ($p < 0.02$, contrast) but no change after application of cTBS or control TMS.

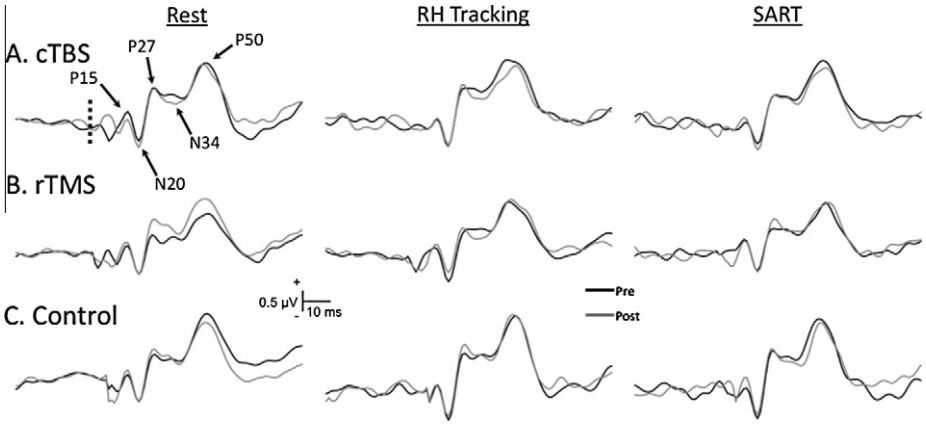

Fig. 1. Grand average waveforms taken from the Cp4 electrode site during Rest, RH Tracking and SART tasks before and after application of (A) cTBS, (B) 1 Hz rTMS and (C) Control rTMS. SEP components of interest are indication by arrows. SEP is time locked to MN stimulation elicited from the left wrist. Dashed line represents MN stimulus onset.

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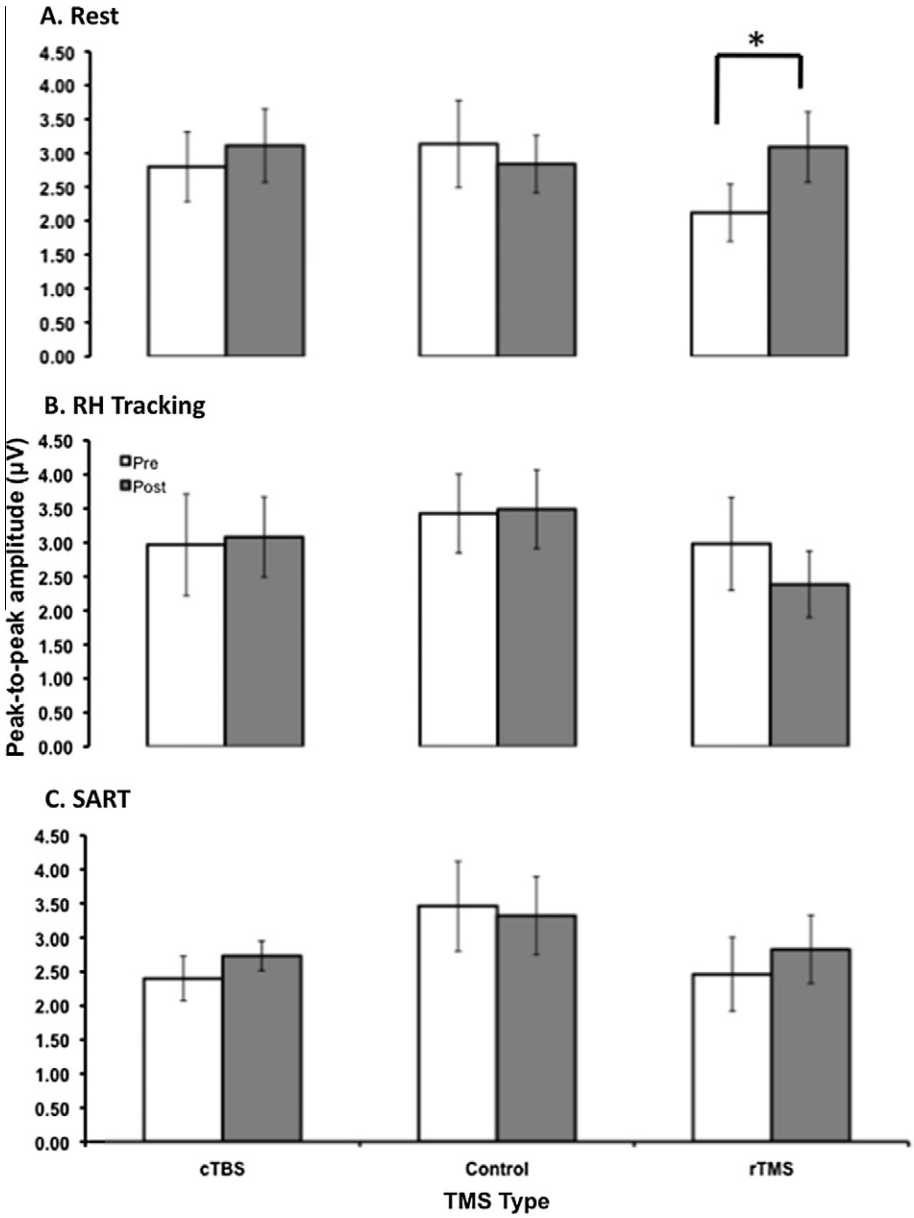

Fig. 2. Mean peak-to-peak amplitudes for the N20–P27 for each condition recorded during (A) Rest, (B) RH Tracking and (C) SART. Peak-to-peak amplitudes were measured from the Cp4 electrode site. Error bars indicate standard errors. * denotes significant contrast, $p < 0.03$.

Table 1
Mean amplitudes of the P15–N20, N20–P27 and N34–P50 peak-to-peak SEP components (mean amplitude, standard error) at the Cp4 electrode site pre and post each TMS variant for each condition.

	Pre			Post		
	P15–N20	N20–P27	N34–P50	P15–N20	N20–P27	N34–P50
Rest						
cTBS	1.71 (0.40)	2.80 (0.51)	3.03 (0.60)	1.58 (0.30)	3.11 (0.54)	3.34 (0.50)
Control TMS	1.61 (0.35)	3.13 (0.64)	3.69 (0.65)	1.84 (0.30)	2.84 (0.42)	3.35 (0.54)
rTMS	1.65 (0.24)	2.12 (0.42)	2.69 (0.32)	1.64 (0.32)	3.09 (0.52)	2.78 (0.42)
RH Tracking						
cTBS	1.46 (0.24)	2.97 (0.75)	2.98 (0.22)	1.45 (0.24)	3.08 (0.59)	3.13 (0.30)
Control TMS	1.77 (0.41)	3.43 (0.58)	3.40 (0.44)	1.72 (0.36)	3.49 (0.58)	3.20 (0.47)
rTMS	1.91 (0.40)	2.98 (0.68)	2.82 (0.28)	1.59 (0.30)	2.38 (0.49)	2.79 (0.30)
SART						
cTBS	1.17 (0.22)	2.40 (0.33)	2.90 (0.43)	1.73 (0.33)	2.73 (0.59)	3.23 (0.47)
Control TMS	1.54 (0.28)	3.46 (0.66)	3.17 (0.53)	1.96 (0.32)	3.32 (0.57)	3.56 (0.53)
rTMS	1.69 (0.31)	2.46 (0.54)	2.75 (0.28)	1.62 (0.29)	2.83 (0.50)	2.77 (0.25)

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None of the two-way repeated measures ANOVAs on N20–P27 amplitude during RH Tracking or the SART task revealed any significant results.

None of the two-way repeated measures ANOVAs on N34–P50 amplitude revealed any significant effects.

3.2. Behavioral performance

For the tracking task the two-way repeated measures ANOVAs for overall RMSE, spatial error RMSE and lag failed to reveal any significant effects. There were no immediate differences in tracking performance for either hand associated with application of cTBS, 1 Hz rTMS or control TMS over S1.

For the SART task the two-way ANOVA upon reaction times revealed a main effect of Time [$F(1, 14) = 4.25$, $p < 0.05$]. The main effect can be attributed to a decrease in the reaction time after application of TMS (mean response times (standard error), pre = 4062 ms (108), post = 3824 (77) ms). In addition the two-way ANOVA upon error rates during the SART revealed a main effect of Time [$F(1, 14) = 6.66$, $p < 0.02$]. The main effect can be attributed to an increase in error rate after application of the TMS (mean error rates (standard error), pre = 26% (2), post = 31% (2)). The increased error rates coupled with the decreased reaction time suggests there was a speed-accuracy trade-off regardless of whether participants received control rTMS, the cTBS or 1 Hz rTMS variants.

4. Discussion

The current study demonstrates the presence of TMS induced interactions between the primary somatosensory cortices as measured using SEPs. Further, our results suggest that interactions between primary somatosensory cortices may be mediated by an intercortical "sensory gating" mechanism rather than intracortical inhibition. Finally, our results show that somatosensory–somatosensory interactions in healthy individuals can be induced by 1 Hz rTMS but that this relationship is dependent upon their relevance to a task.

SEPs elicited from paired-median nerve stimulation are commonly used to assess changes in local cortical excitability in response to an experimental manipulation. This technique normalizes the amplitude of the second SEP of the pair to the first to assess local intracortical excitability by reducing intercortical contributions. While the local effect of TMS might be expected to modify local intracortical excitability in S1 (Ragert et al., 2004, 2008; Tegenthoff et al., 2005), evidence suggests that somatosensory–somatosensory effects may be related, in part, to intercortical contributions involving the dorsolateral prefrontal cortex (DLPFC) and/or the thalamus (Blankenburg et al., 2008; Staines et al., 2002a). By reducing intercortical contributions to changes in cortical excitability, paired-median nerve stimulation may be insensitive to interhemispheric effects that would potentially alter both the SEP to the first and second median nerve stimuli equally.

The increase in N20–P27 amplitude, SEP components localized to Brodmann Areas 3b and 1 of the primary somatosensory cortex (Allison et al., 1991; Desmedt and Tomberg, 1989), after 1 Hz rTMS over the contralateral somatosensory cortex supports an intercortical interhemispheric mechanism that alters early contralateral cortical excitability. This mechanism likely does not involve direct somatosensory–somatosensory callosal connections at the site of stimulation, as Brodmann Areas 3b and 1 are thought to have sparse callosal connections (Iwamura, 2000). Instead the interhemispheric component is likely reflected between areas that can influence primary somatosensory processing, such as secondary somatosensory cortex, DLPFC or the thalamus, where the possibility for interhemispheric interaction is thought to be more prominent. The insensitivity of the N34–P50 SEP component to the TMS intervention suggests that this mechanism may act early in the somatosensory processing hierarchy to control the feedforward flow of sensory afference to areas involved with higher order sensory processing, rather than feedback from these areas, that is based upon a combination of stimulus salience and sensorimotor control.

Two potential pathways for this mechanism may be related to sensorimotor functional connectivity and attention. The former mechanism is likely reflected in the functional connectivity of primary motor and sensory cortex. In this case the increase in N20–P27 amplitude is mediated via transcallosal inhibition between the primary motor cortices such that reducing excitability over ipsilateral S1 results in a lessening of excitatory input to ipsilateral M1 that in turn reduces transcallosal inhibition onto contralateral M1. The reduced transcallosal inhibition subsequently results in increased sensorimotor coupling, and increased sensory cortical excitability, in the contralateral hemisphere at rest.

The latter mechanism is likely reflected in corticocortical inhibition of sensory cortex or corticothalamic excitatory projections from layer VI to thalamic relay nuclei and thalamic reticular nuclei. In this case the contralateral increase in N20–P27 amplitude may reflect a TMS induced disruption of attention that alters the baseline balance of the voluntary attentional network. Reducing ipsilateral somatosensory excitability may have reduced excitatory feedback to ipsilateral DLPFC (Yamaguchi and Knight, 1990; Skinner and Yingling, 1977) that reduced sensory gating in the opposite hemisphere, either through callosal connections between left and right DLFPC or via the thalamus. In both cases the net result is reduced inhibition of contralateral S1 by contralateral DLFPC. Alternatively, it is possible that the increase in contralateral N20–P27 amplitude may reflect a more direct disruption of sensory excitability that reduces excitatory feedback from layer VI of the somatosensory cortex to thalamic relay nuclei (Lam and Sherman, 2010; Pinault, 2004). These corticothalamic projections from layer VI also send excitatory projections to the thalamic reticular nuclei, neurons that send inhibitory projections to both ipsilateral and contralateral thalamic relay nuclei (Pinault, 2004). A reduction in excitability of thalamic reticular nuclei would result reduced inhibition of primary and secondary thalamic relay nuclei, increasing excitability of contralateral S1. These projections have been linked to attentional gating as a method by which sensory afference, at the level of both primary and second thalamic relay nuclei, can be suppressed or enhanced.

The putative sensorimotor functional connectivity and attentional mechanisms that may underpin our results are not mutually exclusive of one another and could in turn feedforward to higher sensory processing areas where additional interhemispheric interaction may result (Iwamura, 2000). While both mechanism may affect early sensory processing, they likely do not operate at the level of primary somatosensory relay to the cortex. Evidence for this supposition comes from the lack of effect of TMS on the P15–N20 peak-to-peak amplitude in the current study. Instead these mechanism(s) likely work at the level of corticocortical transmission from the N20 generator in Brodmann Area 3b to that of the P27 located in Brodmann Area 1, or via secondary thalamocortical projections from the ventroposterior nucleus to Brodmann Area 1. This is inline with previous observations of P27 changes with manipulation of attention (Meehan et al., 2009; Legon and Staines, 2006).

Both a sensorimotor and/or an attentional mechanism can also explain the absence of N20–P27 amplitude changes during right-handed tracking and the SART task. Under a mechanism involving sensorimotor functional connectivity, reductions in left (ipsilateral to the site of TMS stimulation) M1 excitability would be counter-

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acted by increased excitability in left S1 and M1 associated with the requirement to generate a motor response with the right hand. Similarly, under a purely attention mechanism the requirement to extract the relevant sensory re-afference to update motor commands during right-handed tracking or the relevant visual information during the SART task would serve to counteract the TMS induced changes to the underlying voluntary attention network seen during rest.

Interestingly, recent evidence for the absence of reciprocal inhibition between the primary somatosensory cortices (Ishikawa et al., 2007; Eshel et al., 2010) supports, at least in part, a role for pure attentional mechanisms. Recently, Eshel et al. (2010) demonstrated that 10 Hz rTMS over somatosensory cortex improves tactile detection of a median nerve stimulus delivered to the ipsilateral hand but does not impair detection of stimuli delivered to the hand contralateral to the rTMS. A reciprocal inhibition hypothesis predicts that, similar to that observed between ipsilateral and contralateral motor cortex, there should be an inverse relationship between detection thresholds and/or measures of cortical excitability (Schambra et al., 2003). However, the somatosensory TMS literature often demonstrates unilateral effects (Ragert et al., 2004, 2008; Tegenthoff et al., 2005) restricted either to the cortex ipsilateral or contralateral to TMS. The apparent lack of reciprocal inhibition between the somatosensory cortices may reflect a summation of TMS induced changes and the direction of attention to the ipsilateral hand (same side as TMS). In contrast, detection in the hand contralateral to rTMS stimulation might be expected to remain constant as rTMS induced changes are likely to cancelled out by directed attention to the contralateral hand.

Interestingly it appears that, in healthy individuals, cTBS is not sufficient to significantly influence any potential interhemispheric mechanism between the somatosensory cortices. To date only one other study has used single pulse median nerve stimulation to investigate changes in cortical excitability induced by cTBS over the contralateral primary somatosensory cortex (Ishikawa et al., 2007). Similar to the current study, cTBS over left sensory cortex did not induce any change in right somatosensory cortex, despite persistent changes in the left P25/N33 component. It was initially hypothesized that the interhemispheric mechanisms may have been masked by variability in arousal or attention associated with the instructions to the participants (Blankenburg et al., 2008; Meehan et al., 2008; Stefan et al., 2004). However, given the converging results from the current study it is likely that interhemispheric effects are either not elicited or are weaker after cTBS due to differences in the stimulation protocol. This possibility is supported by changes in right S1 cortical excitability after application of rTMS over left M1 (Uguisu et al., 2010) but not after cTBS over left M1 (Ishikawa et al., 2007). Together, these results highlight potential differences in interhemispheric mechanisms between somatosensory and motor cortex. Alternatively it cannot be ruled out that the insensitivity of contralateral SEPs to cTBS over left S1 may be the result of a combination of the lower stimulus intensity and the absence of a concrete method of localization/stimulation threshold definition as is present for M1 (Jung et al., 2008).

Also interesting was that neither cTBS nor 1 Hz rTMS over left S1 produced the expected increase in left-handed tracking performance. Our hypothesis was based upon observations demonstrating changes in perceptual thresholds after peripheral acute deafferentation of the ipsilesional limb (Werhahn et al., 2002a,b; Floel et al., 2008; O'Bryant et al., 2007; Voller et al., 2006). Evidence exists showing that degradation of both tactile discrimination and proprioceptive ability relate to motor learning (Vidoni et al., 2010). There are a number of possible explanations for the lack of behavioral effect upon tracking performance that need to be investigated further. It is clear that there is a functional significance to interhemispheric interactions in visual processing (Hilgetag et al., 2001; Oliveri et al., 1999) that can be extended to motor (Kobayashi et al., 2009) and somatosensory cortex (Seyal et al., 1995). However, despite evidence that perceptual thresholds may improve with TMS over the ipsilateral somatosensory cortex, it does appear, that in the healthy brain, the effects elicited by TMS are not sufficient to improve motor performance in healthy controls within a one-session study. Instead it appears the small benefit to somatosensation associated with the application of TMS in the contralateral hemisphere does not translate to acute increases performance in left-handed tracking. In contrast, the changes observed with peripheral acute deafferentation of the unaffected limb that may produce a small interhemispheric benefit results in larger improvements in performance of the affected limb due to pre-existing decrements in somatosensation. Future work is required to determine if the interhemispheric effects would be visible if 1 Hz rTMS over left S1 was paired with left-handed tracking over multiple sessions.

We did not measure SEPs directly below the site of stimulation or assess tactile perceptual or discrimination thresholds. Therefore, we cannot quantify the effects of TMS upon ipsilateral cortical excitability or any effects upon perception. These choices in experimental design were made for methodological reasons. We chose to remove the electrodes below the site of stimulation from our EEG cap to position our stimulating coil as close to the head as possible and reduce the duration of each session. However, previous research has shown that single pulse SEPs measured over the sensory cortex directly underneath the TMS coil were not influenced by 0.9 Hz rTMS applied over the underlying sensory cortex (Satow et al., 2003), supporting an intracortical mechanism for changes seen at the site of stimulation.

Further, we did not assess tactile perception as these effects have been reported previously and we sought to maximize testing time where the TMS induced effects would be greatest for 1 Hz rTMS (Ziemann et al., 2008). While changes have been shown in both the hand contralateral (Seyal et al., 1995) and ipsilateral (Ragert et al., 2004, 2008; Tegenthoff et al., 2005; Vidoni et al., 2010) we cannot directly relate these results to our study.

The current study is the first to provide converging evidence for TMS induced somatosensory–somatosensory interactions using somatosensory evoked potential evidence. As such it offers further support for an intercortical mechanism relating to the early relay of sensory afference/re-afference mediating functional gains in hemiparetic arm function after peripheral acute deafferentation. In addition, the current study is amongst the first to highlight the importance of task demands and methodological issues, in eliciting interhemispheric effects associated with TMS in the healthy brain.

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