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Continuous theta-burst rTMS over primary somatosensory cortex modulates tactile perception on the hand ☆

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HIGHLIGHTS

- This study is the first examination of the effects of cTBS over primary somatosensory cortex on tactile perception.
- Measures of temporal and spatial tactile acuity were examined using the Cortical Metrics device before and following real and sham cTBS.
- CTBS over SI impairs temporal and spatial tactile acuity for up to 18 min.

ABSTRACT

Objective: Theta-burst stimulation (TBS) over the primary somatosensory cortex (SI) alters cortical excitability, and in its intermittent form (iTBS) improves tactile spatial acuity. The effects of continuous TBS (cTBS) on tactile acuity remain unknown. The present study examined the influence of cTBS over SI on temporal and spatial tactile acuity on the contralateral hand.
Methods: In separate experiments, temporal discrimination threshold (TDT) and spatial amplitude discrimination threshold (SDT) were obtained from the right hand before and for up to 34 min following real and sham cTBS (600 pulses) over left-hemisphere SI.
Results: CTBS reduced temporal and spatial tactile acuity for up to 18 min following real cTBS. Tactile acuity was unaltered in the groups receiving sham cTBS.
Conclusions: CTBS over SI impairs both temporal and spatial domains of tactile acuity for a similar duration.
Significance: CTBS over SI appears to decrease neural activity within targeted cortex and has potential utility in reducing excessive sensory processing.

1. Introduction

Tactile perceptual measures relate to physiological changes in cortical activity within somatosensory, motor and prefrontal cortices and can therefore be used as an indicator of cortical function. Patients with abnormal tactile perception demonstrate abnormalities in primary somatosensory (SI) physiology and/or motor control of the hand (Abbruzzese and Berardelli, 2003; Bara-Jimenez et al., 1998, 2000; Lin and Hallett, 2009; Tinazzi et al., 2009). Further, tactile perceptual impairments may contribute to the severity of motor symptoms in these patient groups (Lee et al., 2005; Shin et al., 2005). Repetitive transcranial magnetic stimulation (rTMS) presents the opportunity to induce physiological changes in SI that may lead to altered tactile perception and potentially modify hand control.

RTMS applied over SI modulates tactile acuity and physiology. Short-lasting impairments in tactile perception are observed with low-frequency rTMS over SI (Knecht et al., 2003; Satow et al., 2003; Vidoni et al., 2010). In contrast, high-frequency rTMS over SI improves tactile acuity (Karim et al., 2006; Pleger et al., 2006; Ragert et al., 2003; Tegenthoff et al., 2005). In addition to perceptual effects, high-frequency rTMS alters SI cortical physiology such that activation is enhanced (Pleger et al., 2006), cortical maps cor-

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responding to the stimulated cortical region are enlarged (Tegenthoff et al., 2005) and paired-pulse somatosensory evoked potential (SEP) inhibition is reduced (Ragert et al., 2004). Importantly, SI physiological changes correlate with alterations in tactile acuity on the hand (Pleger et al., 2006; Tegenthoff et al., 2005).

Compared to repetitive TMS approaches, cTBS offers the opportunity to induce long-lasting changes in cortical excitability using low-intensity stimulation delivered over a short duration (Huang et al., 2005). Intermittent TBS (iTBS) over SI increases SEP amplitude for up to 25 min following stimulation (Katayama and Rothwell, 2007; Katayama et al., 2010; Premji et al., 2010) and has a similar time course of effects on spatial acuity measured using two-point discrimination (Ragert et al., 2008). Continuous TBS (cTBS) over SI appears to have the opposite effect on SEPs with reduced amplitudes persisting up to 13 min following stimulation (Ishikawa et al., 2007). The effects of cTBS on tactile perception have not been examined but if present may have potential clinical applications for patients with excessive sensory processing such as in cerebral palsy and autism (Cascio, 2010). It is also unclear whether cTBS will yield similar effects on both temporal and spatial domains of tactile acuity. Temporal aspects of touch perception are important for transitions from the grip to the lift phase of an object (Johansson and Westling, 1984) while impairments in the spatial domain result in movement detection errors (Gordon and Soechting, 1995). It is the combination of the two domains that contribute to the fine manipulation of tools (Rothwell et al., 1982), tactual identification of objects (Motomura et al., 1990) and tactile exploration of the environment (Jones and Lederman, 2006).

The present study examined the influence of cTBS over left-hemisphere SI on tactile acuity of the contralateral hand. In separate experiments, tactile acuity was assessed by measuring temporal discrimination threshold (TDT) and spatial amplitude discrimination threshold (SDT) using the Cortical Metrics device (CM), a device that yields reliable and objective indices of tactile performance (Folger et al., 2008; Francisco et al., 2008; Tannan et al., 2007a,b; Tommerdahl et al., 2007a,b, 2008). It was hypothesized that real and not sham cTBS applied over SI would impair TDT and SDT for a minimum of 13 min following stimulation in line with the duration of changes in SEP amplitude (Ishikawa et al., 2007).

2. Methods

2.1. Subjects

Eighteen participants were studied, 16 participated in Experiment 1 (mean age = 26 years ± 5.1 years, range = 19–38 years, 7 males), 16 participated in Experiment 2 (mean age = 25 years ± 4.3 years, range = 19–38 years, 7 males) and 14 individuals participated in both. For individuals who participated in both experiments, testing sessions were separated by a minimum of 1 week and these participants received only real or sham TBS in both experiments. The allocation of these participants to the real or sham group for both experiments was necessary to maintain subject naivety about the type of TBS received. Right-handedness was confirmed using a subset of the Edinburgh Handedness Inventory (EHI) (Oldfield, 1971). All subjects gave informed written consent prior to participation. The experiments were approved by the Office of Research Ethics at the University of Waterloo and conformed to the Declaration of Helsinki.

2.2. Electromyography (EMG) recording

Surface EMG was recorded from the first dorsal interosseous (FDI) muscle of the right hand using 9 mm diameter Ag–AgCl surface electrodes. The active electrode was placed over the muscle belly and the reference electrode was placed over the metacarpophalangeal joint of the index finger. EMG was amplified (1000×), bandpass filtered (2 Hz–2.5 kHz, Intronix Technologies Corporation Model 2024F, Bolton, Ontario, Canada), and digitized (5 kHz, Micro1401, Cambridge Electronics Design, Cambridge, UK). Signal software (v 4.02, Cambridge Electronic Design Limited, Cambridge, UK) was used to collect EMG data.

2.3. TMS and neuronavigation

TMS was performed using a MagPro stimulator (MCF-B65; Medtronic; Minneapolis, MN, USA) with 90 mm outer diameter figure of eight coil. Brainsight Neuronavigation software (Rogue Research, Montreal) was used to digitally register the subjects' MRI with the TMS coil. Brainsight Neuronavigation was used to ensure accurate coil placement for the duration of the cTBS (real or sham) stimulation. MRI images were obtained using a 3T General Electric scanner with 172 images acquired with Three-dimensional Ultra Fast Spoiled Gradient Echo Inversion Recovery using a 20 cm field of view (256 × 256). To determine the intensity of cTBS the motor hotspot was first identified within primary motor cortex (M1) that elicited a motor evoked potential (MEP) in the right hand FDI muscle with the coil oriented 45° to the mid-sagittal line. Active motor threshold (AMT) was determined at this location and defined as the lowest intensity required to evoke MEPs of 400 μV amplitude or greater in 5 out of 10 consecutive trials with the FDI contracting to 10% of the subjects maximum voluntary contraction. CTBS was applied using a 600 pulse protocol (i.e. 40 s) used elsewhere (Huang et al., 2005; Ishikawa et al., 2007; Katayama et al., 2010) at 80% AMT over SI, defined as a point 2 cm posterior to the motor hotspot (Ishikawa et al., 2007; Wolters et al., 2005), with the handle oriented backward and laterally at a 45° angle away from midline (Ishikawa et al., 2007; Premji et al., 2010; Ragert et al., 2008). Fig. 1 displays an example of the cTBS coil location in one participant. For sham stimulation the coil was positioned over SI and rotated 90° such that the handle pointed vertically upward while still maintaining scalp contact (Teo et al., 2011).

2.4. Psychophysical tasks

All psychophysical measures were conducted using the Cortical Metrics (CM) device described in detail elsewhere (Tannan et al., 2007a). Using the device, the hand dorsum was placed beneath

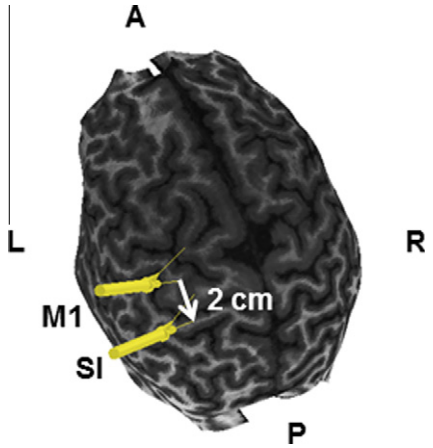

Fig. 1. The motor hotspot for the first dorsal interosseous muscle shown within the primary motor cortex (M1) and the target for TBS within the primary somatosensory cortex (SI) located 2 cm posterior measured using Brainsight Neuronavigation. A (anterior), P (posterior).

two plastic probes that were lowered until a force of 0.1 g was registered. The CM device further indented each probe 500 μm to ensure skin contact prior to stimulation onset. The interprobe distance was set at 32 mm for both experiments to ensure stimuli were delivered to two skin sites beyond the two-point difference limen on the hand dorsum (Tannan et al., 2005a). All CM protocols were designed with LabView (v 8.5, National Instruments Corporation, Texas, USA). Auditory cues were minimized by the use of earplugs in both experiments.

2.5. Experiment 1: effects of cTBS on temporal discrimination threshold (TDT)

Sixteen right-handed participants were studied, eight received real cTBS (mean age = 29, SD = 5.1) and eight received sham cTBS (mean age = 23, SD = 2.6). Trials were collected in blocks of twenty. For each trial, the two probes were vibrated at 25 Hz for 40 ms at an amplitude of 200 μm. The initial trial of each block imposed an interstimulus interval (ISI) of 60 ms between the first and second vibrating probe. The visual display on the computer monitor prompted the participant to report whether they felt the two probes vibrate at the same time (i.e. simultaneously) by selecting the appropriate mouse click (left click = yes, same time, right click = no, non-coincident stimuli) with their left hand. The accuracy of the participants' response determined the adjustment of the ISI for the following trial. The ISI was adjusted by a step-width of 5 ms using a 1 up/1 down response for the first 10 trials and 2 up/1 down for the last 10 (i.e. two correct responses decreased the ISI by 5 ms while one incorrect response increased the ISI by 5 ms), a protocol that provides a reliable and accelerated method to obtain threshold values (Tommerdahl et al., 2007b, 2008). The inter-trial interval was set at 5 s. A schematic of the TDT task is shown in Fig. 2A. The experiment timeline consisted of TDT performed immediately prior to cTBS (real or sham) and at six time intervals following cessation of cTBS (Fig. 2C). For each time interval TDT was calculated as the average of the last five trials (Tommerdahl et al., 2007b, 2008). Prior to testing, three blocks of training trials were performed to familiarize participants with the task and to test whether any learning effects were observed. Each block required participants to obtain five correct consecutive responses in the TDT task. During training visual feedback was given via the computer monitor and indicated to participants whether their response was correct (happy face, 'good job!') or incorrect ('please try again'). The total number of trials required to complete each block of training was tabulated. Performance feedback was only provided during training and not testing trials.

2.6. Experiment 2: effects of cTBS on spatial amplitude discrimination threshold (SDT)

Sixteen right-handed participants were studied with equal numbers in the real (mean age = 28, SD = 4.3) and sham (mean age = 23, SD = 2.6) group. Using the CM device the probes were positioned on the dorsum of the right hand as in Experiment 1 and each time block consisted of 20 trials. For each trial the two probes were vibrated simultaneously at 25 Hz for 500 ms. For the initial trial in each block (i.e. the first trial in each block of 20 trials), the *standard* probe was set at an indentation of 100 μm and the *test* probe was set at 200 μm. The visual display on the computer monitor prompted the participant to report which skin site received the more intense stimulus. Subjects responded with their left hand by selecting the appropriate mouse click (left click = left probe is more intense, right click = right probe is more intense). The accuracy of the participants' response determined the adjustment of the *test* stimulus for the following trial. The amplitude of the *test* probe was adjusted by 10 μm on 1 up/1 down response for the first 10 trials and 2 up/1 down for the last 10 trials (Folger

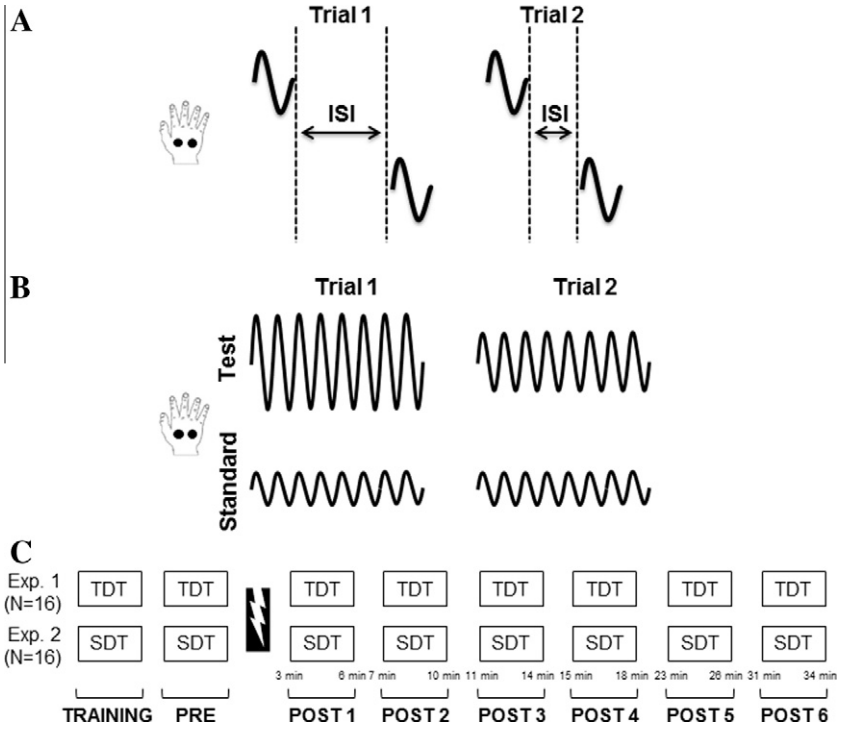

Fig. 2. (A) Temporal discrimination threshold (TDT). Two sequential vibrotactile stimuli were delivered to two distinct skin sites. Two trials shown with subject response from the first trial resulting in a decrease in the interstimulus interval (ISI). (B) Spatial amplitude discrimination threshold (SDT). Two simultaneous stimuli delivered to two distinct skin sites. A greater amplitude of indentation is presented at the *test* site. The *standard* site is always vibrated at 100 μm. The location of the *test* and *standard* vary randomly within a block of trials. Two trials shown with correct subject response resulting in decreasing the amplitude of the *test* probe in the subsequent trial. (C) Timeline for Experiments 1 and 2.

et al., 2008; Tannan et al., 2007a,b, 2008; Zhang et al., 2008). The amplitude of the *standard* probe remained constant at 100 μm throughout all trials. The location of the *standard* and *test* probe (i.e. left or right skin site) was selected randomly by the CM device on a trial-by-trial basis. The inter-trial interval was set at 5 s. A schematic of the SDT task is shown in Fig. 2B. SDT measures were acquired using the timeline from Experiment 1 (Fig. 2C) and were calculated as the average of the last five trials (Folger et al., 2008; Tannan et al., 2007a,b, 2008; Zhang et al., 2008) for each time block. Learning effects and familiarity with the task were examined in three blocks of training trials that required five correct consecutive responses for each block. Visual feedback during training was the same as that in Experiment 1. For the training trials, the total number of trials required to complete each block was summed. Performance feedback was only provided during training and not testing trials.

2.7. Data analysis for Experiments 1 and 2

To assess learning in the training trials, a Friedman test with Bonferroni corrected contrasts (corrected for three comparisons) was conducted for each group (real cTBS, sham cTBS) for both experiments. To assess the influence of cTBS on tactile acuity, a two-way repeated measure analyses of variance (ANOVA) with between subject factor GROUP (2 levels; real cTBS, sham cTBS) and TIME (7 levels; pre, post 1 (3–6 min), post 2 (7–10 min), post 3 (11–14 min), post 4 (15–18 min), post 5 (23–26 min), post 6 (31–34 min)) was performed for TDT (Experiment 1) and SDT (Experiment 2). Post-hoc Tukey's tests were used to identify significance in the event of main effects or interactions. Sphericity was tested with the Huynh–Feldt estimate. All statistical analyses were performed using SAS 9.2 Windows software (SAS Institute Inc., Cary, North Carolina, US). Significance was set at $p \leqslant 0.05$.

3. Results

3.1. Experiment 1: effects of cTBS on temporal discrimination threshold (TDT)

All participants successfully completed the experiment. There were no significant differences in the AMT between the real cTBS (48% ± 10.8 stimulator output) and sham cTBS groups (48.3% ± 6.9)(unpaired *t*-test, $p = 0.926$). The stimulator output for cTBS was on average 38.4% (±8.6). Friedmann's test with Bonferroni correction showed no significant differences among blocks of training for the real cTBS group ($F_{(2,\ 7)} = 3.37$, $p = 0.064$). There was a significant difference during training blocks for the sham cTBS group ($F_{(2,\ 7)} = 8.59$, $p = 0.004$) with an improvement in task performance between block 1 and 2 ($p = 0.011$), and block 1 and 3 ($p = 0.001$). However, by block 3, performance was not significantly different between the two groups (unpaired *t*-test, $p = 0.768$) with an average of 6.1 (±1.5) and 6.4 (±1.8) trials needed to achieve criteria for the real and sham cTBS group, respectively.

The two-way ANOVA revealed a significant interaction between GROUP and TIME ($F_{(6,\ 84)} = 2.99$, $p = 0.011$) without main effects of GROUP ($F_{(1,\ 84)} = 1.21$, $p = 0.29$) or TIME ($F_{(6,\ 84)} = 1.37$, $p = 0.234$). Fig. 3A plots the group-averaged TDT (with standard errors) and Table 1 describes the individual subject data for the real and sham groups. Post-hoc Tukey's test revealed that TDT values were significantly higher at time blocks post 1 (3–7 min, $p = 0.001$) and post 4 (15–18 min, $p = 0.013$) compared to pre-cTBS. The group-averaged TDT (with standard deviation) for all trials is shown in Fig. 3B for the real cTBS group. As can be seen, performance for all time blocks plateau by approximately trial 10. Further, the influence of cTBS is observed once performance reaches threshold levels (~trial 10 and later) and not at earlier trials when discrimination performance uses suprathreshold ISIs (~trials 1 through 9).

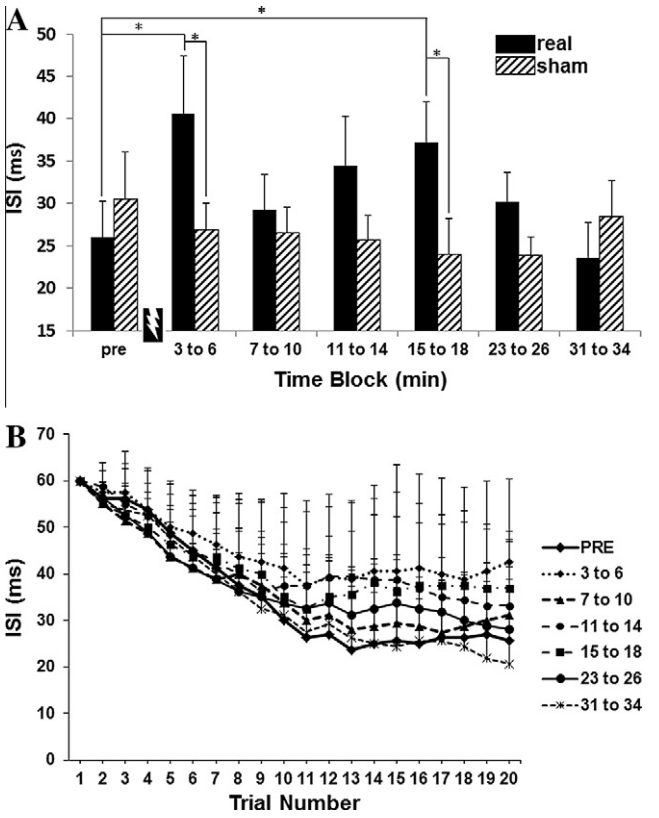

Fig. 3. Effect of cTBS on TDT. (A) Group-averaged TDT (with standard errors) for real and sham groups before and at each time block following cTBS. $^{*}p \leqslant 0.05$. (B) Group-averaged temporal discrimination performance for each trial in each time block for the real cTBS group.

3.2. Experiment 2: effects of cTBS on spatial discrimination threshold (SDT)

All participants successfully completed the experiment. The intensity to achieve AMT was similar in the real (49.3% (±8.3)) and sham cTBS (45.9% (±2.7)) groups (unpaired *t*-test, $p = 0.391$). The mean stimulator output for cTBS delivery was 39.3% (±6.6). Friedmann's test with Bonferroni correction showed a significant difference among blocks of training for the real cTBS group ($F_{(2,\ 7)} = 8.37$, $p = 0.012$) with an improvement in task performance between block 1 and 3 ($p = 0.012$). There were no significant differences between training blocks for the sham cTBS group ($F_{(2,\ 7)} = 1.08$, $p = 0.366$). Performance between the two groups was not significantly different by block 3 (unpaired *t*-test, $p = 0.199$) with an average of 9 (±6.2) and 6 (±1.1) trials needed to achieve criteria for the real and sham cTBS group, respectively.

The two-way ANOVA revealed significant main effects of GROUP ($F_{(1,\ 84)} = 7.30$, $p = 0.017$), TIME ($F_{(6,\ 84)} = 2.97$, $p = 0.011$) and an interaction between GROUP and TIME ($F_{(6,\ 84)} = 2.33$, $p = 0.039$). Fig. 4A plots the group-averaged data (with standard errors) for the SDT difference limens (the difference between the *test* and *standard* probe amplitude) and Table 1 displays the individual subject data for the real and sham groups. Post-hoc Tukey's test revealed that compared to pre-cTBS, SDT values were significantly higher at post 1 (3–6 min, $p = 0.0003$), post 2 (7–10 min, $p = 0.004$), post 3 (11–14 min, $p \leqslant 0.0001$), and post 4 (15–18 min, $p \leqslant 0.0001$). The average of the SDT tracking data is shown in Fig. 4B for the real cTBS group (with standard deviations) and re-

Table 1
Individual subject data for psychophysical thresholds for all tasks and groups.

Subjects	Gender	Age	Pre	Post 1	Post 2	Post 3	Post 4	Post 5	Post 6
TDT (ms): real cTBS									
1	F	29	29	39	33	33	31	35	29
2	M	27	27	28	34	24	44	34	14
3	F	27	25	59	21	39	43	29	26
4	M	27	40	54	33	39	41	29	27
5	M	38	11	38	30	20	35	31	21
6	F	25	8	25	19	24	28	15	9
7	F	24	26	12	13	26	15	21	16
8	M	36	42	70	51	71	61	48	47
Average ± SE		29 ± 5.1	26 ± 4.3	40.6 ± 6.8	29.3 ± 4.1	34.5 ± 5.8	37.3 ± 4.8	30.3 ± 3.5	23.6 ± 4.1
TDT (ms): sham cTBS									
1	F	25	23	31	31	32	31	27	27
2	F	24	24	31	21	37	10	23	24
3	F	21	25	14	14	21	23	19	29
4	F	27	19	19	21	25	18	14	17
5	M	21	66	39	32	15	7	32	32
6	M	22	21	19	41	35	26	21	54
7	M	19	25	25	31	18	36	23	16
8	F	23	41	37	21	23	41	32	29
Average ± SE		22.8 ± 2.6	30.5 ± 5.6	26.9 ± 3.2	26.5 ± 3.1	25.8 ± 2.9	24 ± 4.2	23.9 ± 2.2	28.5 ± 4.2
SDT (μm): real cTBS									
1	F	29	20	162	46	112	112	50	122
2	M	27	23	9	46	56	14	30	9
3	F	27	48	70	58	46	50	28	28
4	M	27	30	78	104	76	98	22	50
5	F	24	15	76	50	90	62	60	64
6	M	38	78	100	100	126	112	116	80
7	M	26	20	84	88	94	140	78	14
8	F	26	28	32	42	42	68	62	9
Average ± SE		28 ± 4.3	32.8 ± 7.4	76.4 ± 16.1	66.8 ± 9.2	80.3 ± 10.9	82 ± 14.4	55.8 ± 11	47 ± 14.2
SDT (μm): sham cTBS									
1	F	25	36	34	34	92	46	78	74
2	F	21	19	12	26	13	9	12	15
3	F	27	14	80	98	11	32	58	62
4	M	21	42	56	36	68	42	28	38
5	M	22	42	50	16	18	15	12	28
6	M	19	46	32	14	9	15	34	11
7	F	24	18	28	68	48	78	52	10
8	F	23	35	18	34	14	9	11	15
Average ± SE		23 ± 2.6	31.5 ± 4.5	38.8 ± 7.9	40.8 ± 10.1	34.1 ± 11.2	30.1 ± 8.5	35.6 ± 8.8	31.6 ± 8.7

veals that tracking performance becomes increasingly altered by cTBS when performance approaches threshold (i.e. trials 15–20). However, effects of cTBS are also modestly observed at the suprathreshold test probe intensities (i.e. trials 1 through 14).

4. Discussion

The present study demonstrated reduced temporal and spatial tactile acuity on the right hand following cTBS over left-hemisphere SI. Threshold changes occurred in the first time block following cTBS and persisted for up to 18 min, modestly exceeding the duration of cTBS effects on SEPs (Ishikawa et al., 2007). Tactile acuity was unaltered following sham cTBS over SI. To our knowledge, these are the first experiments to reveal the modulating effects of cTBS on tactile acuity.

The neural mechanisms that mediate spatial discrimination involve a combination of excitation and inhibition within and between adjacent SI cortical columns, respectively (Friedman et al., 2008). In the SDT task presented, two skin sites are vibrated simultaneously and the magnitude of excitation in the corresponding cortical columns relates to the intensity of stimulation; an increase in stimulus intensity yields greater excitation within a cortical column (Chen et al., 2003; Simons et al., 2005) which improves the opportunity to detect the stimuli (Jones et al., 2007). Excitation of these columns results in lateral inhibition (Sripati et al., 2006), with the greatest amount located between two peaks of excitation (Gardner and Costanzo, 1980a,b). The summed lateral inhibition between the peaks allows for the distinction between the two spatially segregated skin sites (Laskin and Spencer, 1979; Tannan et al., 2005b). Importantly, the extent and duration of lateral inhibition increases with a greater magnitude of excitation within the activated cortical column (Chen et al., 2003; Friedman et al., 2008). Following cTBS, we observed that a more intense *test* probe (i.e. greater amplitude) was necessary to correctly identify the spatial location of the skin site that received the more intense stimulation. CTBS may induce this effect by suppressing the underlying excitability within SI cortical columns, thereby reducing the spatial extent of lateral inhibition and the concomitant segregation of the peaks of excitation. At a perceptual level, these neural events would decrease the opportunity to detect the amplitude of either stimulus. Increasing the amplitude of the *test* probe improved detection following cTBS likely via restoring the required lateral inhibition between the two peaks of excitation. In contrast, iTBS improves tactile spatial acuity (Ragert et al., 2008) and may act to increase the underlying cortical excitability and increase the spatial extent of stimulus-evoked lateral inhibition thereby promoting the segregation of the peaks of excitation. Therefore, one suggestion is that iTBS enhances inhibitory processes that act to differentiate between peaks of excitation. In support of this suggestion, FMRI BOLD signals within the sensorimotor cortex decrease following iTBS over M1 (Cardenas-Morales et al., 2010). In the temporal discrimination task presented, the first skin site stimulated activates its corresponding cortical columns within SI. If a second

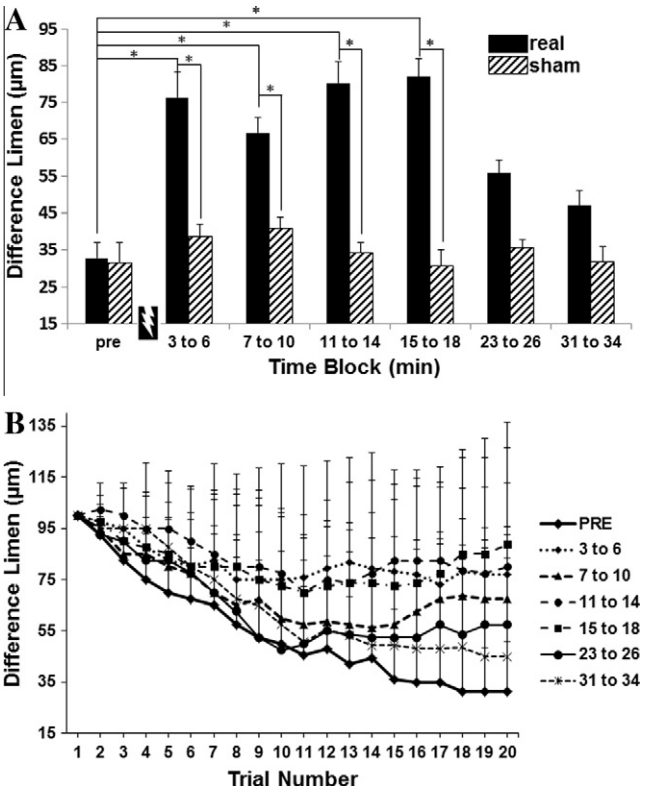

Fig. 4. Effect of cTBS on SDT. (A) Group-averaged SDT (with standard errors) for real and sham groups before and at each time block following cTBS. $^{*}p \leqslant 0.05$. (B) Group-averaged spatial amplitude discrimination performance for each trial in each time block for the real cTBS group.

skin site within close spatial proximity is stimulated shortly thereafter, detection of the second input may be compromised due to the lateral inhibition created by the first stimulus located within the columns that receive input from the second skin site (Gardner and Costanzo, 1980a,b). However, with a greater delay between the onset of the first and second stimuli, the lateral inhibition created by the first stimulus dissipates (Gardner and Costanzo, 1980b) allowing the second stimulus to excite its corresponding cortical columns more fully thereby increasing the opportunity for its detection (Laskin and Spencer, 1979). Following cTBS, a longer delay is necessary to identify the first and second stimulus as non-coincident. Similar to the SDT task, this effect may occur if

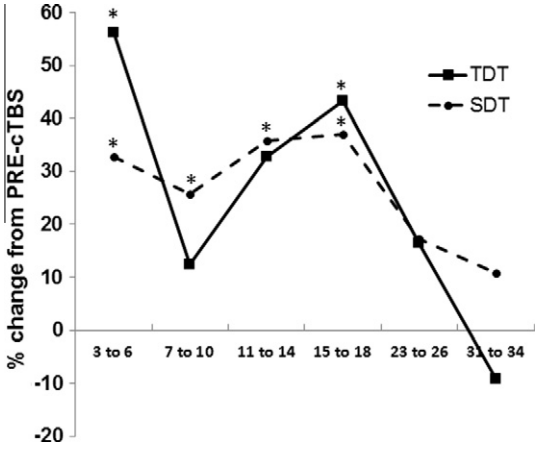

Fig. 5. Time course of cTBS induced effects for TDT and SDT experiments. Percent change from pre-cTBS of the group-averaged means for the real cTBS groups from both experiments. Significance ($^{*}p \leqslant 0.05$) is based on comparisons within each experiment (i.e. pre versus post in SDT or pre versus post in TDT).

cTBS reduces the excitability of SI cortical columns. If true, detection of the second skin site may be further compromised due to reduced excitation of the corresponding columns and the presence of lateral inhibition generated by the first input. With a longer delay between the two stimuli, the decreased level of excitability due to the cTBS remains, however, the lateral inhibition dissipates increasing the opportunity to detect the presence of the second stimulus. Additional explanations for the action of cTBS on SDT and TDT may involve direct effects on inhibitory interneurons (Benali et al., 2011; Stagg et al., 2009) that mediate lateral inhibition between columns.

The time course of changes in the TDT and SDT experiments were remarkably similar as is shown in Fig. 5. TDT was significantly altered at 3–6 and 15–18 min while SDT was altered continuously from 3 to 18 min. Further, threshold values at post block 2 (7–10 min) show impairments that are less than those in the preceding and following time blocks. The explanation for the variability is not clear, however, this finding highlights the complexity of the cTBS–neuronal interactions that are exposed by sampling data at frequent intervals. The variability in the time course would have been missed had longer testing intervals been used. Last, thresholds from both tasks reveal a return to pre-cTBS values at ~23 min following cTBS, in line with the short-lasting effects observed in SEP studies (Ishikawa et al., 2007; Premji et al., 2010). For both tactile domains, we examined the influence of cTBS on the limits of tactile acuity and it is clear from Figs. 3B and 4B that the greatest influence is observed when performance is at threshold level. However, it is notable that suprathreshold performance in the spatial but not temporal task appears to be modestly impaired by cTBS.

TDT values were 26 ms before cTBS, similar to that reported elsewhere (Hoshiyama et al., 2004; Tommerdahl et al., 2007b) and increased to 40 ms following cTBS. Despite the increase in threshold, the magnitude of the impairment remains far less than that observed in most clinical populations. Focal lesions within SI or subcortical structures result in an average TDT of 173 ms (Lacruz et al., 1991). TDT ranges from 95 to 155 ms in focal hand dystonia (Bara-Jimenez et al., 2000; Fiorio et al., 2003; Sanger et al., 2001) and from 78 to 95 ms in Parkinson's disease (PD) (Artieda et al., 1992; Fiorio et al., 2008). However, in autism TDT is ~37 ms (Tommerdahl et al., 2008), similar to the value obtained following cTBS in our healthy controls. Autism is associated with the reduction in GABAergic inhibition between cortical columns which can act to impair the lateral inhibitory mechanisms (Casanova et al., 2003) and may explain the increased TDT thresholds in this group. Prior to cTBS, SDT required a difference limen of ~32 μm, in line with other reports in healthy subjects (Folger et al., 2008; Francisco et al., 2008; Tannan et al., 2007a,b; Zhang et al., 2008) and increased to 82 μm at the time of greatest impairment following cTBS. A similar increase in SDT is observed in focal hand dystonia compared to aged-match controls (~33% increase) (Bara-Jimenez et al., 2000) although a larger impairment is seen in PD (Sathian et al., 1997). Therefore it appears that cTBS is capable of inducing impairments that approach levels seen in some but not all clinical groups. It may be that cTBS at alternate intensities would evoke impairments of greater magnitude.

The present experiments examined changes in tactile perception following cTBS over left SI. Previous research has investigated the effects of cTBS over SI on SEPs and has related the suppressed SEP amplitudes to changes in neuronal processing within the targeted cortical area (Ishikawa et al., 2007; Katayama et al., 2010). There appears to be a relationship between changes in SEPs and tactile perception such that an increase in SEP amplitude is associated with an increase in tactile acuity (Hoffken et al., 2007; Werhahn et al., 2002) while a decrease in SEP amplitude is associated with a decrease in tactile acuity (Staines et al., 2002; Tamura et

al., 2008). One study has examined both SEPs and tactile perception following iTBS and noted an improvement in tactile acuity and an increase in cortical excitability as measured through a reduction of paired-pulse SEP suppression (Ragert et al., 2008). The results of the present study are aligned with the direction of effects exhibited through changes in SEP amplitude following cTBS.

Research has emphasized the importance of improving tactile acuity through high-frequency rTMS (Karim et al., 2006; Pleger et al., 2006; Ragert et al., 2003; Tegenthoff et al., 2005), iTBS (Ragert et al., 2008) and tactile co-activation paradigms (Godde et al., 2000). These results have applications in clinical populations who demonstrate diminished tactile acuity (i.e. PD, focal hand dystonia). However, in the present study we emphasize the importance of diminishing tactile acuity and there are certain clinical groups who could potentially benefit from such outcomes. Cerebral palsy is associated with hyper-responsiveness to tactile stimuli (Cascio, 2010). Patients with prefrontal damage have difficulty inhibiting task-irrelevant information and exhibit deficient sensory gating, processes mediated in part by SI (Knight et al., 1999). Last, patients with autism may demonstrate diminished tactile acuity (Tommerdahl et al., 2007a, 2008) but may also exhibit hyper-sensitivity to tactile stimulation (Cascio, 2010). Low-frequency rTMS over prefrontal cortex in autism improves sensory gating with the enhancement of task-relevant stimuli and the suppression of task-irrelevant stimuli (Sokhadze et al., 2010). Identifying methods to reduce tactile acuity may prove beneficial in such patients. However, it remains unknown whether cTBS over SI in autism or other disorders presenting with hyper-sensitivity will demonstrate acuity impairments similar to our control group.

There are limitations that could influence the interpretation of the present study. First, although cTBS was applied over SI it remains unknown whether the induced acuity changes were due to direct effects of TMS within SI or to effects in additional remotely connected loci. Temporal and spatial discrimination are associated with activation in secondary somatosensory cortex, premotor and prefrontal cortex, inferior parietal lobule, basal ganglia, cerebellum and supplementary motor area (de Lafuente and Romo, 2006; Lacruz et al., 1991; Pastor et al., 2004; Rao et al., 2001) and changes in the neural activity of these loci may have contributed to the observed impairments. Second, we observed a different pattern of results between the sham and real cTBS groups during the training trials in both experiments. Although performance was similar across both groups by the final block of training, it remains unclear whether cTBS induced impairments may be graded by the rate or overall magnitude of learning achieved during training. Third, the group receiving real cTBS was slightly older (~5–6 years) than the sham group for both experiments. However, this difference is unlikely to alter the results since the 'pre' TDT and SDT values did not differ between groups and the slightly older group is unlikely to exhibit age-related declines in tactile acuity or processing. Last, tactile acuity was measured on the hand dorsum to reduce variability between subjects that would result from use dependent plasticity (Serino and Haggard, 2010). However, future studies may probe the influence of cTBS on volar skin surfaces such as the digit tips and reveal changes similar to those seen in tactile co-activation paradigms (Godde et al., 2000). It is notable that TDT values are similar from the dorsum and digit tips (Tommerdahl et al., 2007b) though the magnitude or time course of cTBS effects may be different between the two skin sites.

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