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Research article

Time-course of pain threshold after continuous theta burst stimulation of primary somatosensory cortex in pain-free subjects

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ABSTRACT

Primary somatosensory cortex (S1) is involved in pain processing and thus its suppression using neuromodulatory techniques such as continuous theta burst stimulation (cTBS) might be a potential pain management strategy in patients with neuropathic pain. cTBS over S1 is known to elevate pain threshold in young adults. However, the time course of this after-effect is unknown. Furthermore, the effect of cTBS over S1 on pain threshold might be confounded by changes in the excitability of primary motor cortex (M1), an area known to be involved in pain processing, due to spread of current. Therefore, whether S1 plays a role in pain processing independent of M1 also remains unknown. The corticospinal excitability (CSE) can provide a measure of M1 excitability because cTBS over M1 is known to reduce CSE. Here, we studied the time-course of the effects of MRI-guided cTBS over S1 on electrical pain threshold (EPT) and CSE. Ten healthy young adults received cTBS over S1 and sham stimulation in counterbalanced sessions at least 5 days apart. EPT and CSE were recorded before and following cTBS over S1. We assessed each measure once before stimulation and then every 10 min starting immediately after stimulation until 40 min. cTBS over S1 elevated EPT compared to sham stimulation with the after-effect lasting for 40 min. We observed no change in CSE following cTBS and sham stimulation. Our findings suggest that cTBS over S1 can elevate EPT for 40 min without altering M1 excitability.

1. Introduction

Understanding the cortical mechanisms underlying pain processing is of considerable interest to guide the design of effective pain management strategies using neuromodulatory techniques [1,2]. Neuroimaging studies have suggested the involvement of cortical areas such as dorsolateral prefrontal cortex, primary somatosensory cortex (S1), secondary somatosensory cortex (S2), and primary motor cortex (M1) in the processing of painful stimuli [1–3]. Transcranial magnetic stimulation (TMS) has been used to test the critical role of these areas in pain processing [1–4]. For instance, theta burst-induced disruption of S1 has been shown to produce analgesic effects in able-bodied individuals, thus suggesting the causal involvement of S1 in pain processing [1]. Continuous theta burst stimulation (cTBS; a form of repetitive theta burst TMS), over S1 significantly reduced the perception of CO_2 laser-evoked painful stimuli assessed immediately after stimulation delivered to the contralateral hand when compared to the ipsilateral hand [1]. However, the time course of analgesic after-effect of S1 cTBS on pain threshold remains unknown.

Due to the proximity of S1 and M1 regions, it is plausible that TMS over S1 could lead to concomitant activation of M1 by inducing current in the neighboring M1 region [5,6] and/or directly via S1-M1 connections [7,8]. As disruption in M1 activity is also known to produce analgesic effects in patients with chronic pain [9,10], the finding of elevated pain threshold reported following cTBS over S1 might be confounded by the changes in M1 excitability. Therefore, whether S1 plays a role in pain processing independent of M1 remains unknown. We studied the time-course of after-effect of cTBS delivered to S1 on electrical pain threshold (EPT) in healthy young adults using a sham-controlled, crossover design. Because cTBS over M1 is known to reduce corticospinal excitability (CSE) for at least 30 min [11–13], we hypothesized that the after-effect of cTBS over S1 on EPT will last for at least 30 min without affecting M1 excitability. We addressed the possibility of current spread to M1 by assessing changes in CSE following

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S1 cTBS because CSE is sensitive to changes in M1 excitability at rest [13–15].

2. Materials and methods

2.1. Subjects

Ten healthy, young, right-handed [16] subjects (mean ± SD: 25.30 ± 4.81 years; 4 females) provided written informed consent to participate in two experimental sessions separated at least 5 days apart. The two sessions that included a sham stimulation session were counterbalanced across subjects. Subjects self-reported no history of neurological or musculoskeletal disorder. The study was approved by the Institutional Review Board of the University of Houston.

2.2. Quantitative sensory testing

Electrical sensory threshold (EST) and electrical pain threshold (EPT) were measured using manual triggering of electrical stimulator (DS7A; Digitimer, Hertfordshire, UK) via a surface bar electrode placed over the abductor pollicis brevis (APB) muscle. For the EST measurement, the intensity of electrical stimulation was started from zero and gradually increased in steps of 0.1 mA until the subject explicitly felt electrical stimulation. This was followed by the EPT measurement. The intensity was started from the EST and increased in steps of 1 mA until the subject first felt the electrical stimulation to be painful. Participants were explicitly instructed that the aim of the study was not to assess maximum pain they can bear but to measure only their pain threshold. To improve consistency among subjects, they were advised to report a stimulus to be painful upon experiencing the pain level equivalent to 1 on the 0–10 visual analog scale [17]. Three repetitions were made for each measure and the corresponding average was used for both EST and EPT measures. Tactile sensitivity (TS) was measured using Semmes-Weinstein Monofilaments Examination (SWME, Smith and Nephew Roland, Menominee Falls, WI) [17–20]. Tactile sensibility thresholds were obtained from the distal volar pads of the index finger. The index finger was tested approximately midway between the center of the pad and the radial margin of the finger. A threshold was recorded for the smallest filament diameter (buckling force in mg, according to the manufacturer's calibration) that could be perceived on at least 70 % of its applications. We assessed EPT, EST, and TS measures once before cTBS (PRE) and then every 10 min starting immediately following cTBS ($POST_0$) until 40 min ($POST_{10}$, $POST_{20}$, $POST_{30}$, $POST_{40}$).

2.3. Transcranial magnetic stimulation

We measured CSE by assessing the size of motor evoked potentials (MEP) elicited in the first dorsal interosseous muscle (FDI) of the right hand. The FDI muscle activity was recorded using differential surface electrodes (Delsys Bagnoli EMG System, Boston, MA). The data were sampled at 5 kHz using CED data acquisition board (Micro1401, Cambridge, England).

Single-pulse TMS was used to assess CSE over primary motor cortex (M1) during the experiment [21,22]. We first estimated the resting motor threshold (rMT) by delivering suprathreshold single monophasic TMS pulses (Magstim 200, Whitland, UK). The TMS coil was held tangential to the scalp and perpendicular to the presumed direction of the central sulcus, 45° from the midsagittal line, with the handle pointing backward, inducing current in the posteroanterior direction. The coil position was adjusted to optimize the motor-evoked potential (MEP) in the FDI muscle. Following this procedure, the rMT was estimated as the minimum TMS-intensity to elicit motor evoked potential (MEP) with an amplitude of ~50 μV (peak-to-peak) for at least 5 of the 10 consecutive trials in the FDI muscle [15,21,23,24]. The TMS coil was stabilized using a coil holder mounted on the TMS chair (Rogue Research). The TMS coil was traced on the subject's scalp using a surgical marker pen. The coil location was regularly checked for any displacement that might have occurred during a session. The average rMT across subjects (mean ± SE) was 54 ± 3 % of the maximum stimulator output. The corticospinal excitability (CSE) was assessed with the intensity set at 120 % of rMT over the identified FDI region and averaged across 10 consecutive trials [25]. To avoid contamination of pre-stimulus EMG, we instructed the subjects to avoid making hand movements during the trials. This was visibly confirmed during the session by closely monitoring pre-stimulus EMG activity. Furthermore, trials with EMG activity greater than two times the standard deviation of the mean background EMG activity occurring 100 ms before the TMS pulse were excluded (< 2 % of trials) [21].

2.3.1. Continuous theta burst stimulation

We estimated active motor threshold (aMT) to set the stimulation intensity of continuous theta burst stimulation. For aMT estimation, subjects were instructed to exert 20 % of their maximum voluntary force (MVF) on a grip device instrumented with force transducers (Nano-25; ATI Industrial Automation, Garner, NC, 1 kHz sampling rate) with the tips of index finger and thumb using visual feedback provided on a computer monitor [26]. Each subject was instructed to grip the device as hard as possible for one second followed by a break (~1 min). This procedure was repeated three times, and we used the largest grip force as the MVF recorded across three trials [26]. The aMT was determined as the TMS intensity that induced 200 μV peak-to-peak MEPs in 5 of 10 trials in the FDI muscle during force production at 20 % of MVF [27]. The aMT was 44 ± 2 % (mean across all subjects ± SE; n = 10) of the maximum stimulator output.

We used continuous theta burst stimulation (cTBS) to disrupt left primary somatosensory region representing the contralateral hand. Prior to the cTBS procedure, we obtained a high-resolution T1-weighted MRI scan (3 T Philips Ingenia scanner) for each subject. A three-dimensional brain was reconstructed from the MRI slices to display the cortical surface (Brainsight software, Rogue Research Inc., Canada). For S1 cTBS, we positioned the TMS coil over the postcentral gyrus posterior to the M1 FDI hotspot [15,28]. The mean Montreal Neurological Institute coordinates of the stimulation sites for left S1 were -41.67 ± 8.90, -28.27 ± 6.57, 65.10 ± 11.06 (x, y, z, mean ± SD; n = 10).

We delivered cTBS over the left S1 using a figure-of-eight coil at 80 % of aMT to temporarily disrupt its activity and generate a 'virtual lesion'. Repetitive biphasic TMS pulses were delivered in the form of bursts of three pulses at 50 Hz at a rate of 5 Hz, i.e. 200 ms inter-burst interval, for 40 s. The cTBS protocol resulted in the delivery of 600 pulses [13]. The exact positioning of the coil was visually monitored throughout the stimulation duration. For sham stimulation ($cTBS_{SHAM}$), same stimulation parameters were used, but the coil was placed perpendicular over the left S1 region so that no relevant current flow was induced in the cortical tissue [29,30]. The intensity of stimulation was well within the safety guidelines for TMS use [11–13,15,31–34].

2.4. Statistical analysis

We used repeated measures analysis of variance ($\alpha = 0.05$) with within-subject factors of CONDITION ($cTBS_{S1}$, $cTBS_{SHAM}$) and TIME (PRE, $POST_0$, $POST_{10}$, $POST_{20}$, $POST_{30}$, $POST_{40}$). We used Levene's test for the homogeneity of variance assumption. In case of unequal variance ($P < 0.05$), we performed repeated measures Friedman non-parametric test ($\alpha = 0.05$). Posthoc comparisons performed using paired *t*-test or non-parametric Wilcoxon signed-rank test were corrected for multiple comparisons using the false discovery rate at $p < 0.05$. To investigate whether modulation in EPT is associated with modulation in MEP amplitude, we performed Pearson product-moment correlation analysis between the change in MEP amplitude at each time point following stimulation in relation to PRE with the change in EPT at each time point following stimulation with relation to PRE.

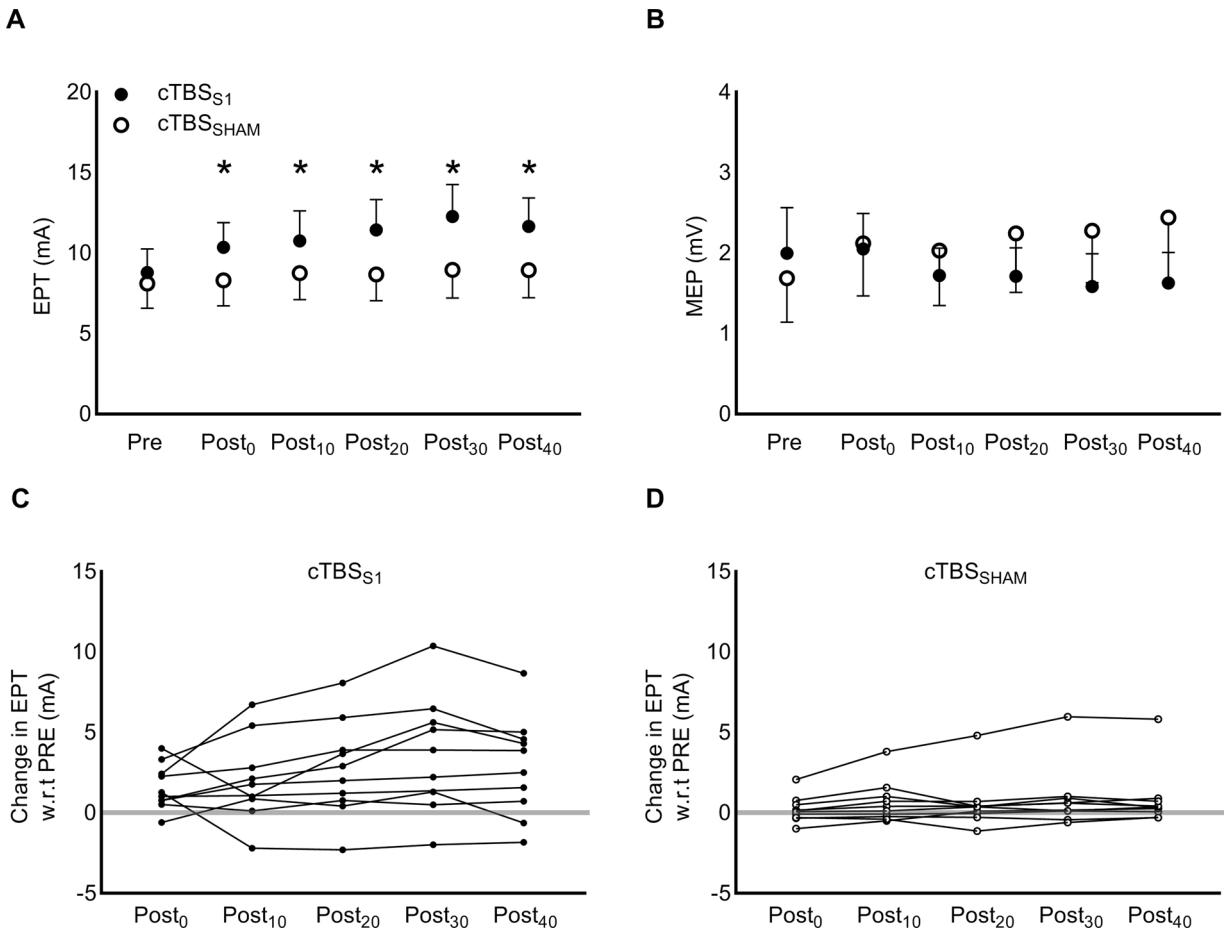

Fig. 1. Time course of electrical pain threshold (EPT) and corticospinal excitability (CSE) post cTBS over S1. **A.** Increase in EPT following cTBS over S1 compared to sham stimulation (significant *Condition* × *Time* interaction: p = 0.011*)*. Asterisks indicate a significant increase in EPT at Post time point with respect to PRE (p < 0.05, FDR-corrected). **B.** No change in group-level data for CSE assessed over M1 following cTBS$_{S1}$ and cTBS$_{SHAM}$. For **A** and **B**, each circle and error bar represent mean and standard error across subjects (n = 10) respectively for the given time-point. **C.** Subject-wise time course of change in EPT with respect to PRE following cTBS over S1 (solid circles). **D.** Subject-wise time course of change in EPT with respect to PRE following sham stimulation (open circles).

3. Results

No subjects reported any side effects during or after the experimental sessions.

We found a significant increase in EPT following cTBS$_{S1}$ when compared to cTBS$_{SHAM}$ (CONDITION × TIME interaction: $F_{5,45} = 3.37$, $p = 0.011$, $\eta_p^2 = 0.27$; Fig. 1**A**). Following cTBS$_{S1}$, EPT increased from PRE to Post$_0$ ($t_9 = 3.56$, $p = 0.006$), Post$_{10}$ ($t_9 = 2.43$, $p = 0.038$), Post$_{20}$ ($t_9 = 2.85$, $p = 0.019$), Post$_{30}$ ($t_9 = 3.12$, $p = 0.012$), and Post$_{40}$ ($t_9 = 2.96$, $p = 0.016$). There was no change in EPT following cTBS$_{SHAM}$ (all $t_9 < 1.57$, all $p > 0.15$; refer Fig. 1**C** and 1**D** for subject-wise changes in EPT). There was no difference in PRE EPT between cTBS$_{S1}$ and cTBS$_{SHAM}$ ($t_9 = 0.68$, $p = 0.51$).

We found no difference in MEP amplitude across cTBS$_{S1}$ and cTBS$_{SHAM}$ (no CONDITION × TIME interaction: $F_{5,45} = 2.24$, $p = 0.07$, $\eta_p^2 = 0.19$; no CONDITION effect: $F_{1,9} = 1.39$, $p = 0.27$ $\eta_p^2 = 0.13$; no TIME effect: $F_{5.45,} = 0.23$, $p = 0.95$, $\eta_p^2 = 0.03$; Fig. 1**B**). There was no difference in PRE MEP amplitude between cTBS$_{S1}$ and cTBS$_{SHAM}$ ($t_9 = 1.6$, $p = 0.14$). Moreover, there was no correlation between changes in MEP amplitude (although insignificant) and EPT following cTBS over S1 ($r = 0.194$; $p = 0.17$) and sham stimulation ($r = 0.014$; $p = 0.91$). These findings indicate that the stimulation current delivered over S1 did not affect CSE.

We found that TS reduced following cTBS$_{S1}$ (main effect of TIME for nonparametric Friedman test, $\chi^2_{5,10} = 15.174$, $p = 0.010$; Fig. 2**A**). Posthoc comparisons were conducted using Wilcoxon signed-rank test and the change in TS from PRE to Post$_0$ ($Z = -1.826$, $p = 0.068$), Post$_{10}$ ($Z = -2.21$, $p = 0.02$), Post$_{20}$ ($Z = -2.21$, $p = 0.02$), POST$_{30}$ ($Z = -2.032$, $p = 0.042$) and POST$_{40}$ ($Z = -1.841$, $p = 0.066$) failed to reach the FDR corrected significance level. We did not find a change in TS following cTBS$_{SHAM}$ (no main effect of TIME, $\chi^2_{5,\ 10} = 8.582$, $p = 0.127$). There was no difference in PRE TS measure between cTBS$_{S1}$ and cTBS$_{SHAM}$ (Wilcoxon signed-rank test: $Z = -1.000$, $p = 0.317$).

PRE EST measure was not different between cTBS$_{S1}$ and cTBS$_{SHAM}$ ($t_9 = 0.203$, $p = 0.844$). We observed a significant increase in EST following stimulation (main effect of TIME: $F_{5,45} = 7.112$, $p < 0.001$, $\eta_p^2 = 0.441$). However, this increase was similar following cTBS$_{S1}$ and cTBS$_{SHAM}$ (no CONDITION × TIME interaction: $F_{5,45} = 1.378$, $p = 0.250$, $\eta_p^2 = 0.133$; no main effect of CONDITION: $F_{1,9} = 0.493$, $p = 0.500$, $\eta_p^2 = 0.052$; Fig. 2**B**).

4. Discussion

We studied the time-course of the effect of cTBS over S1 on electrical pain threshold (EPT) in healthy young adults. Our findings suggest that cTBS over S1 can elevate EPT for 40 min in healthy young adults without any change in M1 excitability. Previous studies have investigated the effect of cTBS over S1 on pain threshold but the time course of pain threshold post cTBS has remained unclear [1,3,46]. For instance, Torta et al. [1] found a reduction in the perception of nociceptive CO_2 laser thermal stimuli delivered to the contralateral hand immediately following cTBS over S1. In contrast, Poreisz et al. [3]

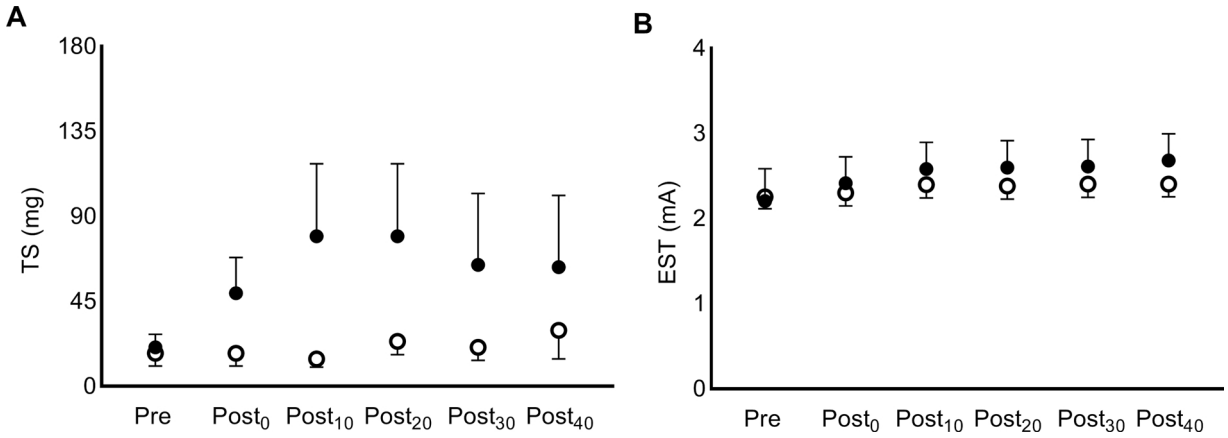

Fig. 2. Time course of tactile sensitivity (TS) and electrical sensory threshold (EST) post cTBS.**A.** Persistent elevation in TS post $cTBS_{S1}$ but not $cTBS_{SHAM}$. **B.** Temporal drift in EST following both – $cTBS_{S1}$ and $cTBS_{SHAM}$ sessions. Each circle and error bar represents mean and standard error across subjects (n = 10) respectively.

administered cTBS over S1 but failed to notice a change in the perception of painful laser thermal stimuli delivered to the contralateral hand following cTBS. Instead, they found attenuation of the N2 component of laser-evoked potentials (LEP) about 5 min following cTBS over S1. However, these studies investigated the modulation in pain threshold only once, i.e., either immediately [1] or 5 min [3] following cTBS over S1. To the best of our knowledge, our study provides first evidence for a longer lasting after-effect of a single session of cTBS over S1 on electrical pain threshold in healthy young adults.

The time course of the effects of cTBS over S1 on the electrophysiological changes within S1 has been reported earlier [14]. Specifically, cTBS over S1 reduced the amplitude of parietal P25/N33 components of somatosensory potentials evoked as a result of electrical stimulation of the median nerve with the after-effect lasting for 13 min [14]. The P25/N33 component arises from the superficial area 1 situated in the crown of the postcentral gyrus [35]. Because the neuronavigation-guided cTBS in our study was directed to the crown of the postcentral gyrus, the increase in EPT following cTBS might have resulted from disruption of the superficial area 1 of S1. The longer lasting after-effect of cTBS over S1 on EPT (40 min) versus somatosensory-evoked potentials (13 min, [14]) might be due to disruption of pain processing within distant cortical and subcortical regions through the spread of current [12,36,37]. The processing of pain engages a widespread network consisting of S1, secondary somatosensory cortex, anterior cingulate cortex, insula, prefrontal cortex, thalamus, cerebellum, nucleus accumbens, and amygdala [9,38–40]. Therefore, cTBS over S1 might have disrupted activity within one or more of these brain regions. Functionally, the role of S1 in pain processing has been discussed in the context of encoding temporal aspects of pain memory as well as extracting location and intensity information from the nociceptive signals [41–43]. cTBS over S1 in the present study could have influenced one or more of these processes which, in turn, could have led to elevated pain threshold. In summary, our findings suggest that cTBS over S1 can serve as a potential neuromodulatory tool for pain management. The long-term effect after repetitive use of this intervention and its application in clinical populations need further investigation.

In this study, we also investigated the involvement of M1 following cTBS over S1. S1 and M1 are reciprocally connected [7,8] via direct monosynaptic connections [44]. It has been shown that the synaptic inputs from S1 to M1 are stronger than the inputs from M1 to S1 [44]. As evoked activity in S1 due to a sensory stimulus has been found to subsequently propagate to M1 [45], we considered the possibilities that the spread of cTBS current might either take a direct path from S1 to M1 or an indirect path through the scalp [6,37]. In either case, modulation of activity within M1 following cTBS over S1 would have influenced the corticospinal excitability as assessed over M1 [11,13,14]. In clinical settings, M1 cTBS is known to affect pain perception in patients with chronic pain [9,10]. However, in healthy individuals, the findings have been mixed. For instance, a recent study failed to show any change in the ratings of nociceptive stimuli with different strengths following cTBS over M1 [47]. In contrast, another study reported reduced perception of nociceptive stimuli post cTBS over M1 [1]. In our study, the cTBS current from S1 did not spread to M1 as suggested by no change in the corticospinal excitability following cTBS over S1. Moreover, there was no association between changes (although insignificant) in MEP size and changes in EPT following S1 cTBS. These findings suggest that the observed effects of cTBS over S1 on EPT were not due to the involvement of M1. Future studies should be directed to determine the effects of cTBS over S1 on a wider network involved in pain processing.

Besides EPT, we also investigated the effects of cTBS over S1 on tactile sensitivity and electrical sensory threshold. Tactile sensitivity reduced following cTBS over S1, but not following sham stimulation, a finding consistent with previous studies [48–50]. As noted above, the after-effect on tactile sensitivity might be due to the disruption of superficial area 1 of S1. Although repeated measures analysis could detect a reduction in tactile sensitivity, pair-wise post hoc comparisons failed to reach the corrected significance level. Thus, we are unable to comment on the time-course of the after-effect of cTBS over S1 on tactile sensitivity. Interestingly, we found that both cTBS and sham stimulation increased electrical sensory threshold. The increase in electrical sensory threshold following sham stimulation might suggest habituation to repeated low intensity electrical stimulation of the thenar eminence [51]. It is likely that similar habituation to low intensity electrical stimulation was present in the cTBS session which may have confounded the effects of cTBS over S1 on electrical sensory threshold. Therefore, the electrical sensory threshold, at least in our study, was not a reliable measure to study the effects of cTBS over S1 on sensory perception. It is important to note that similar habituation was not observed for other experimental measures such as EPT, MEP, and tactile sensitivity. One limitation of our study is relatively fewer healthy participants included. Future studies may consider recruiting a larger sample to investigate between-subject variability in EPT responses.

In summary, the findings from this study suggest that disruption of S1 using neuronavigated cTBS can increase the electrical pain threshold in healthy young adults with the effect lasting for 40 min. The observed analgesic after-effect was not due to the involvement of M1. These findings underscore the role of S1 in pain rehabilitation for future studies aimed at elucidating mechanisms underlying pain processing.

CRediT authorship contribution statement

Nishant Rao: Conceptualization, Data curation, Formal analysis,

Investigation, Methodology, Visualization, Writing - original draft, Writing - review & editing. **Yen-Ting Chen:** Conceptualization, Methodology, Investigation, Writing - review & editing. **Regan Ramirez:** Formal analysis, Investigation, Writing - review & editing. **John Tran:** Investigation, Writing - review & editing. **Sheng Li:** Conceptualization, Methodology, Resources, Writing - review & editing. **Pranav J. Parikh:** Conceptualization, Methodology, Resources, Supervision, Project administration, Funding acquisition, Formal analysis, Visualization, Data curation, Writing - review & editing.

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