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Continuous Theta Burst Stimulation of the Supplementary Motor Area: Effect Upon Perception and Somatosensory and Motor Evoked Potentials

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ABSTRACT

Background: The supplementary motor area (SMA) has been implicated in many aspects of movement preparation and execution. In addition to motor roles, the SMA is responsive to somesthetic stimuli though it is unclear exactly what role the SMA plays in a somatosensory network.
Objective/Hypothesis: It is the purpose of this study to assess how continuous theta burst stimulation (cTBS) of the SMA affects both somatosensory (SEPs) and motor evoked potentials (MEPs) and if cTBS leads to alterations in tactile perception thresholds of the index fingertip.
Methods: In experiment 1, cTBS was delivered over scalp sites FCZ (SMA stimulation) ($n = 10$) and CZ (control stimulation) ($n = 10$) in separate groups for 40 s (600 pulses) at 90% of participants' resting motor threshold. For both groups, median nerve SEPs were elicited from the right wrist at rest via electrical stimulation (0.5 ms pulse) before and at 10 min intervals post-cTBS out to 30 min ($t =$ pre, 10, 20, and 30 min). Subjects' perceptual thresholds were assessed at similar time intervals as the SEP data using a biothesiometer (120 Hz vibration). In experiment 2 ($n = 10$) the effect of cTBS to SMA upon single and paired-pulse MEP amplitudes from the right first dorsal interosseous (FDI) was assessed.
Results: cTBS to scalp site FCZ (SMA stimulation) reduced the frontal N30 SEP and increased tactile perceptual thresholds 30 min post-stimulation. However, parietal SEPs and MEP amplitudes from both single and paired-pulse stimulation were unaffected at all time points post-stimulation. cTBS to stimulation site CZ (control) did not result in any physiological or behavioral changes.
Conclusion(s): These data demonstrate cTBS to the SMA reduces the amplitude of the N30 coincident with an increase in vibration sensation threshold but does not affect primary somatosensory or motor cortex excitability. The SMA may play a significant role in a somatosensory tactile attention network.

Introduction

The supplementary motor area (SMA) is classically associated with various aspects of movement preparation and execution [1]. In addition to these motor roles the SMA has been demonstrated to be responsive to somesthetic stimuli in primates [2,3] and humans [4,5]. The SMA receives peripheral afferent input via the thalamus [6] and from post-rolandic parietal areas [7,8] supporting a role for the SMA in a somatosensory network. In addition, SMA responsiveness to peripheral afferent input is inferred by the N30 frontal somatosensory evoked potential elicited by electrical median nerve stimulation [9]. It is unclear however, exactly what role the SMA plays in a somatosensory network though the SMA has been identified as part of a tactile attention network [5] and hypothesized to link somatic sensation to action [10]. Further, lesion of the SMA has been associated with impairment in a temporal discrimination task [11]. Transcranial magnetic stimulation (TMS) of the SMA has been shown to disrupt various aspects of motor performance [12–14] and to affect motor cortex excitability [15,16] but no literature to date has explored how transient inhibition of the SMA using TMS affects somatosensory evoked potentials and tactile perception. In contrast, there are numerous papers exploring how magnetic stimulation of the primary somatosensory [17–25], parietal [26,27] and motor cortex [17,20,28] affects tactile perception.

TMS protocols similar to those that affect behavioral performance delivered to both M1 and S1 also modulate somatosensory evoked potentials [25,29–31]. Continuous theta burst stimulation (cTBS) [32] delivered over both primary motor and somatosensory

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cortex has been shown to also affect median nerve somatosensory evoked potentials but with differing effects. cTBS over M1 resulted in an increase of N30 amplitude and parietal SEP components whereas cTBS of S1 suppressed the same components [33]. Unfortunately, none of the above studies investigated both tactile perceptual thresholds and SEP effects and specifically effects upon the frontal N30.

The frontal N30 SEP is a large negative potential recorded maximally over frontal central scalp electrode sites and as such has been suggested to be generated by the underlying cortex, most notably the SMA [9], though an exact generator has not yet been established. The N30 is likely generated independently of parietal potentials as it is spared with an S1 lesion [34] and specifically attenuated as a result of meningioma of the falx cerebri compressing the SMA [35]. It is hypothesized that N30 amplitude is largely the result of proprioceptive afference [36,37] and previous research suggests a link between N30 amplitude and sensorimotor integration independent of parietal potentials as it is particularly affected in Parkinson's disease [38], is facilitated during movement of the contralateral limb [39,40] but attenuated by motor imagery or ideation tasks [41].

The purpose of this study was twofold: 1) to investigate how transient inhibition of the SMA using cTBS affects the frontal N30 somatosensory evoked potential and further, to determine if this results in any perceptual consequences, and 2) to test if cTBS of the SMA affects motor cortex excitability as a possible means of somatosensory effects. It was hypothesized that inhibitory stimulation of the SMA would attenuate the frontal N30 and that such attenuation of somatosensory input to the SMA would be accompanied by alterations in tactile perceptual measures. Furthermore, it was expected that cTBS of the SMA would attenuate the amplitude of MEPs.

Methods

Participants

A total of 27 subjects participated in the two experiments. Two groups of subjects participated in experiment 1 on separate days. Each group consisted of 10 participants (4 female, age 24 $\pm$ 3.6 yrs), (3 female, age 23 $\pm$ 3.3 yrs). Three participants were included in both groups. Ten subjects participated in experiment 2 (3 female; 25.6 $\pm$ 4.6 yrs) performed on separate days from experiment 1 to test the effects of cTBS to SMA on motor cortical excitability. All subjects were self-report right hand dominant and provided written informed consent to participate. None reported any history of neurological or musculoskeletal impairments or any contraindicators for TMS. All were paid a nominal fee for their participation. The University of Waterloo Office of Research Ethics approved all experimental procedures.

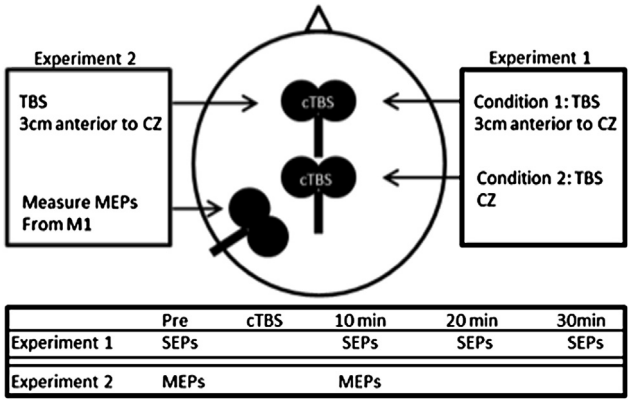
Experiment 1 – SEP and perceptual detection

Behavioral task

Participants were seated in a desk chair with elbow and forearm of both arms resting on a platform upon a tabletop. The platform allowed for the hand to rest over the far edge in slight flexion of the wrist and allowed for a comfortable resting of the index finger upon a vibrating post-placed at the end of the raised platform. Individual somatosensory thresholds were determined on the right index finger using the method of limits with a Vibratron II biothesiometer (Physitemp Instruments, Clifton, NJ, USA) (120 Hz vibration) for all time points of testing (pre-cTBS, 10, 20, and 30 min). To ensure that subjects were not using a time estimation strategy to report perception, the timing of displacement increase was random and non-increase catch trials were interspersed amongst true increases. All subjects performed the tactile judgment task with their eyes closed. Participants were familiarized with the vibration sensation before testing and instructed to relax and not move their finger or arm and to be sure they felt the vibration before reporting it. To establish a pre-testing baseline, participants repeated the threshold testing until three consecutive trials were within one vibration unit of each other. Vibration units (X) are related to the true amplitude (A) of post-excursion in microns by the following formula: $A = (0.5)\,X^2$. Participants were not informed of these values at any point of the testing and were naïve to the purposes of the study. For each time point of testing post-cTBS, 3 repeats of the tactile judgment were performed resulting in one average value. Vibration threshold testing was performed pre-cTBS (10 min prior) and at time points 10, 20, and 30 min post-cTBS (see Fig. 1).

Stimulation and recording

SEPs were derived from the electrical stimulation of the median nerve of the dominant wrist. Square wave pulses of 0.5 ms duration (GRASS S88 stimulator with SIU5 stimulus isolation unit; West Warwick, Rhode Island, USA) were delivered through a bar electrode, with the anode distal, fixed over the median nerve. Stimulation occurred at a constant rate of 1 Hz and at an intensity sufficient to produce a small but noticeable thumb twitch. Surface electromyography (EMG) was recorded from the thenar musculature to record the M-wave, an EMG wave resulting from the direct stimulation of the motoneuronal axons serving the thenar musculature to ensure consistency of stimulation. EMG recordings were amplified (2000×), band-pass filtered (20–200 Hz), digitized and stored for later analysis. Electroencephalographic (EEG) data were recorded from two Ag–AgCl cup electrodes fixed to the scalp and referenced to the linked mastoids. One electrode was placed 3 cm anterior to site CZ and the other over a spot corresponding to electrode site CP3 (contralateral to MN stimulation) in accordance with the international 10–20 system for electrode placement. Data were amplified (40,000×), filtered (2–200 Hz) and digitized at 1000 Hz (NeuroScan 4.3; Compumedics; Charlotte, NC, USA). SEPs were extracted by averaging epochs time-locked to median nerve stimulation (−50 to 300 ms). All traces were visually inspected for artifact (blinks, eye movements or contraction of scalp musculature) and any contaminated epochs were eliminated before averaging. All traces were the result of 200 randomly chosen stimulations. Electrodes were removed during the cTBS



	Pre	cTBS	10 min	20 min	30min
Experiment 1	SEPs		SEPs	SEPs	SEPs
Experiment 2	MEPs		MEPs		

Figure 1. Experimental setup. Pictorial representation (not to scale) of coil placement(s) and time-line for each experiment. Experiment 1 examined the effect of continuous theta burst stimulation (cTBS) to scalp sites FCZ (3 cm anterior to CZ) and CZ upon somatosensory evoked potentials (SEPs). Experiment 2 examined the effect of cTBS to FCZ upon motor evoked potentials (MEPs) derived from the left primary motor cortex (M1). The bottom box outlines the time of respective recordings. (Pre) prior to cTBS and at times 10, 20, and 30 min post-cTBS.