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Continuous theta-burst stimulation over primary somatosensory cortex modulates short-latency afferent inhibition

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HIGHLIGHTS

- 30 Hz continuous theta-burst stimulation (cTBS) over primary somatosensory cortex (SI) reduces short-latency afferent inhibition (SAI) between 45 and 60 min following stimulation.
- SAI reduction and motor-evoked potential facilitation following SI cTBS follow a similar time course and may therefore share similar neural mechanisms.
- cTBS over SI versus primary motor cortex has opposite effects on corticospinal excitability.

ABSTRACT

Objective: The present study investigated the effects of continuous theta-burst stimulation (cTBS) over primary somatosensory (SI) and motor (M1) cortices on motor-evoked potentials (MEPs) and short-latency afferent inhibition (SAI).
Methods: MEPs and SAI were recorded from the first dorsal interosseous (FDI) muscle of the right hand following 30 Hz cTBS over left-hemisphere SI and M1 delivered to the same participants in separate sessions. Measurements were taken before and up to 60 min following cTBS.
Results: CTBS over M1 suppressed MEPs and did not alter SAI. In contrast cTBS over SI facilitated MEPs and decreased median and digital nerve evoked SAI.
Conclusions: These findings indicate that SAI amplitude is influenced by cTBS over SI but not M1, suggesting an important role for SI in the modulation of this circuit. These data provide further evidence that cTBS over SI versus M1 has opposite effects on corticospinal excitability.
Significance: To date, plasticity-inducing TMS protocols delivered over M1 have failed to modulate SAI, and the present research continues to support these findings. However, in young adults, cTBS over SI acts to reduce SAI and simultaneously increase corticospinal excitability. Future studies may investigate the potential to modulate SAI via targeting neural activity within SI.

1. Introduction

Motor evoked potentials (MEPs) elicited via Transcranial magnetic stimulation (TMS) are reduced when preceded by electrical stimulation of a peripheral nerve approximately 20–25 ms earlier (Tokimura et al., 2000). This phenomenon is known as short-latency afferent inhibition (SAI) and is considered to be mediated via acetylcholine (Ach) (Di Lazzaro et al., 2000) at the level of the

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cortex (Tokimura et al., 2000). SAI is modulated by dopamine (Sailer et al., 2003), and $GABA_A$ agonist lorazepam reduces SAI (Di Lazzaro et al., 2005b). SAI interacts with other neural circuits that are driven by GABAergic interneurons such as short-interval intracortical inhibition (Alle et al., 2009), short-interval interhemispheric inhibition (Tsutsumi et al., 2012) and long-interval intracortical inhibition (Udupa et al., 2009). Further, SAI evoked by mixed (i.e. median) and cutaneous (i.e. digital) nerves may be somatotopically dependent whereby muscles which are innervated by the stimulated nerve produce a greater degree of SAI than non-innervated muscles (Classen et al., 2000). For instance, digits in closer proximity to the digital nerve stimulated produce a greater degree of SAI (Tamburin et al., 2001).

The magnitude of SAI is modifiable. SAI is increased with spatial attention controlled by a counting task (Kotb et al., 2005). In contrast, SAI can be selectively reduced in specific movement or pre-movement phases during finger tasks (Asmussen et al., 2013; Voller et al., 2006). Depending on the pre-movement phase, decreases in SAI may be driven via cortical or spinal mechanisms (Asmussen et al., 2013). Repetitive TMS (rTMS) may also alter SAI. Low-frequency rTMS applied over primary somatosensory cortex (SI) reduces SAI in focal dystonia but does not alter SAI in healthy controls (Baumer et al., 2007). Over M1, rTMS decreases MEPs without changing SAI (Fischer and Orth, 2011). Intermittent theta burst stimulation (iTBS) applied to M1 increases SAI in Parkinson's disease (PD) patients on medication without altering SAI in controls (Zamir et al., 2012). Identifying a method such as cTBS to modify SAI may provide new therapeutic approaches for modulating abnormal sensorimotor circuitry in specific clinical populations such as stroke and dystonia.

Continuous theta burst stimulation (cTBS) applied over M1 decreases MEPs (Goldsworthy et al., 2012) but increases MEPs when applied over SI (Jacobs et al., 2012, 2013) and higher-order somatosensory area 5 (Premji et al., 2011). The present study investigated the effects of 30 Hz cTBS delivered over left-hemisphere SI and M1 on SAI and MEPs measured from the first dorsal interosseous muscle (FDI) of the right hand. CTBS at 30 Hz delivered over M1 results in less inter-subject variability and longer lasting effects compared to the traditional 50 Hz cTBS (Goldsworthy et al., 2012). It was hypothesized that MEPs will be decreased for up to 25 min and increased for up to 45 min following cTBS over M1 and SI, respectively (Goldsworthy et al., 2012; Jacobs et al., 2013).

2. Methods

2.1. Participants

Eighteen individuals (7 Males, Mean age = 21 ± 2.0, range of 19–25) participated. All participants were right handed as determined by a subset of the Edinburgh Handedness Scale (Oldfield, 1971). In Experiment 1, all participants completed two experimental sessions separated by a minimum of one week. In Experiment 2, nine subjects that were in Experiment 1 returned to participate (1 Male, mean age, SD, range = 20.4 ± 1.9, 19–25). This study was approved by the McMaster Research Ethics Board and conformed to the Declaration of Helsinki.

2.2. Electromyography (EMG) recording

Surface electrodes (9 mm diameter Ag-AgCl) were used to record electromyography (EMG) from the first dorsal interosseous (FDI) muscle of the right hand in a bipolar montage with the active electrode placed over the muscle belly and the reference electrode placed over the metacarpophalangeal joint of the index finger. Electromyography was band-passed filtered between 20 Hz and 2.5 kHz and amplified ×1000 (Intronix Technologies Corporation Model 2024F with Signal Conditioning; Intronix Technologies Corporation, Bolton, Canada) and digitized at 5 kHz by an analog-to-digital interface (Power1404; Cambridge Electronics Design, Cambridge, UK).

2.3. Neuronavigation and Transcranial magnetic stimulation (TMS)

Single pulse TMS was delivered with a custom-built 50 mm diameter figure-of-eight branding coil connected to a Magstim 200^2 stimulator (Magstim, Whitland, UK). The motor hotspot for the FDI was determined over left-hemisphere M1. The hotspot was identified as the optimal location with the lowest threshold and most consistent responses isolated in relaxed FDI of ~1 mV MEP amplitude. The figure-of-eight coil was positioned over the motor hotspot at ~45 degrees to the mid-sagittal plane to induce a posterior-to-anterior monophasic current in the cortex. The motor hotspot was marked by digital registration using a standard MRI template via Brainsight 2 Neuronavigation (Rogue Research, Montreal, Canada). This motor hotspot and the 50 mm figure-of-eight branding coil were used for all measures of MEPs and SAI.

CTBS was applied using a Magstim Super Rapid stimulator (Magstim, Whitland, Dyfed, UK) connected to a figure-of-eight air cooled coil with the handle pointed 45 degrees to the mid-sagittal plane to induce the first current in the cortex in the posterior-to-anterior direction. The cTBS protocol is a modified version of the original protocol (Huang et al., 2005). The modified cTBS consisted of 3 stimuli (bursts) applied at intervals of 33.3 ms (30 Hz) repeated at 16.7 ms intervals (6 Hz) as described by Goldsworthy et al. (2012). Resting motor threshold (RMT) was defined as the minimum stimulus intensity required to evoke MEPs with amplitude $\geqslant$50 μV in 5 out of 10 consecutive trials whilst the subject is quiescent (Siebner and Rothwell, 2003). CTBS was delivered at 70% of RMT over the target location within M1 or SI. Within M1, cTBS was delivered over the FDI hotspot. For SI, cTBS was delivered over a position 2 cm posterior to the M1 hotspot using Brainsight 2 Neuronavigation (Rogue Research Inc., Montreal, Canada). RMT was collected with the biphasic pulses of the Magstim Super Rapid stimulator and air-cooled coil.

2.4. Experiment 1: SAI and MEPs following cTBS over M1 or SI

2.4.1. Somatosensory evoked potentials (SEPs)

SEPs were used to determine the N20 latency for each subject. The N20 potential represents arrival of somatosensory afference to area 3b (Allison et al., 1991). This latency was then used to adjust the ISI for SAI of each subject for SI and M1 sessions. Subjects were seated in a relaxed position during SEP acquisition. SEPs were recorded over left-hemisphere SI following electrical stimulation of the right median nerve at 3 Hz. The median nerve was stimulated using a surface bar electrode (square wave pulse, 0.2 ms duration) at the right wrist (Grass SD 9, Grass Technologies, West Warwick, USA) with the cathode proximal to the anode. Median nerve stimulation was set to motor threshold defined as the minimum intensity to elicit a slight thumb twitch. The active electrode was placed at C3′ located 2 cm posterior to C3 (Nuwer et al., 1994) and referenced to electrode Fpz (International 10–20 System) with the ground electrode placed on the skin overlying the left clavicle. EEG recordings were amplified 10 K and filtered from 2 to 2500 Hz (Intronix Technologies Corporation Model 2024F with Signal Conditioning, Bolton, Canada). Electrode impedances were maintained at <5 kΩ (UFI Checktrode, Model 1089 Mk III, UFI, Morro Bay, USA). Five hundred stimuli were delivered and time-locked averaged off-line.