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Research report

Speed of processing in the primary motor cortex: A continuous theta burst stimulation study

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HIGHLIGHTS

- Primary motor cortex may play an integral role in modulating the excitability of corticospinal response characteristics.
- Effects of continuous theta burst stimulation on the primary cortex are highly variable.
- Behavioral responses are attenuated in the limb contralateral to site of theta burst stimulation.
- Primary motor cortex may play a greater role in mediating reaction time following higher intensity stimulation.

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ABSTRACT

'Temporally urgent' reactions are extremely rapid, spatially precise movements that are evoked following discrete stimuli. The involvement of primary motor cortex (M1) and its relationship to stimulus intensity in such reactions is not well understood. Continuous theta burst stimulation (cTBS) suppresses focal regions of the cortex and can assess the involvement of motor cortex in speed of processing. The primary objective of this study was to explore the involvement of M1 in speed of processing with respect to stimulus intensity. Thirteen healthy young adults participated in this experiment. Behavioral testing consisted of a simple button press using the index finger following median nerve stimulation of the opposite limb, at either high or low stimulus intensity. Reaction time was measured by the onset of electromyographic activity from the first dorsal interosseous (FDI) muscle of each limb. Participants completed a 30 min bout of behavioral testing prior to, and 15 min following, the delivery of cTBS to the motor cortical representation of the right FDI. The effect of cTBS on motor cortex was measured by recording the average of 30 motor evoked potentials (MEPs) just prior to, and 5 min following, cTBS. Paired *t*-tests revealed that, of thirteen participants, five demonstrated a significant attenuation, three demonstrated a significant facilitation and five demonstrated no significant change in MEP amplitude following cTBS. Of the group that demonstrated attenuated MEPs, there was a biologically significant interaction between stimulus intensity and effect of cTBS on reaction time and amplitude of muscle activation. This study demonstrates the variability of potential outcomes associated with the use of cTBS and further study on the mechanisms that underscore the methodology is required. Importantly, changes in motor cortical excitability may be an important determinant of speed of processing following high intensity stimulation.

1. Introduction

The use of reaction time as a primary outcome variable in the assessment of corticospinal tract integrity is commonplace [1–4]. Reaction time is often used as an indicator of a wide range of mental faculties including cognitive ability [3,5], short- and long-term memory [6,7], attentional processes [5,8,9], and the connectivity of parallel and serial processing pathways. The latencies required for external stimuli to be perceived, processed and translated into a

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motor command have been heavily researched and are considered to be well understood. However, there are documented examples of reaction times that appear to occur outside the range of what would typically be considered normal [10–12]. Currently, there is little understanding of the variability of reaction time data within an individual as well as between individuals and tasks, and a number of unique stimulus characteristics including modality, prior familiarity, response congruence, and intensity have been proposed as potential determinants of reaction time.

Certainly, there exist a number of locations along the sensorimotor pathway that may be involved in the modulation of reaction time. Premotor and primary motor areas are most notably involved in the selection and preparation of movement [13] and excitability between these regions has been implicated in modulation of choice reaction time [14]. The primary motor cortex (M1), due to the convergence of excitatory and inhibitory activity and because of its direct projections to descending pyramidal tract fibers as well as indirect connection to somatosensory relays in the thalamus [15], likely plays an important role in the modulation of reaction time. Specifically, a reduction in the required threshold for activation or an increase in the rate of rise excitability in the motor cortex in temporally urgent situations may assist in reducing reaction time based on the demands of the stimulation.

Stimulus intensity has long been demonstrated to have a profound effect on reaction time [16–20], although the direct contribution of central nervous system (CNS) areas that may be involved in this intensity-based modulation has not been fully understood. Previous work utilizing electroencephalography (EEG) demonstrated that event related potentials (ERP) relative to a high intensity, non-noxious electrical stimulation evoked a large negativity centralized over pre-motor areas approximately 75 ms prior to the onset of muscle activity in a simple reaction time task [21]. This negativity was not observed following a low intensity stimulus and reaction times were significantly slower in this condition, which suggested that frontal cortical areas may be specifically receptive to the intensity of the stimulus and may influence the reaction time.

Repetitive transcranial magnetic stimulation (rTMS) is a commonly used, non-invasive method of stimulating the brain of human subjects *in vivo*. Depending on the pattern of the TMS pulse delivery, facilitatory or inhibitory effects on the stimulated site can be observed. Of particular interest in the current study is the use of continuous theta burst stimulation (cTBS), in which a total of 600 sub-active motor threshold pulses are focally delivered over a period of 40 s at 3 pulses at 50 Hz, repeated every 200 ms [22]. Although the specific CNS mechanism behind the effects of cTBS is not yet fully understood, it is hypothesized that this pattern of pulses temporarily reduces the effectiveness of synaptic connections, thus requiring a greater excitatory input to depolarize in response to synaptic propagation, resulting in an inhibitory effect [22–24]. The effects of such synaptic attenuation over the M1 can be observed by comparing motor evoked potentials (MEPs) at the effector contralateral to the stimulated site both prior to and after a bout of cTBS. Additionally, the effects of cTBS result in facilitation of MEP amplitude [25] and somatosensory excitability [26] in the non-stimulated cortex, indicative of inhibitory and facilitatory mechanisms between the hemispheres, which may have important implications for the speed of processing relative to the non-stimulated limb.

Previously, Huang et al. [22] demonstrated increased reaction times in response to cTBS over the contralateral motor cortex representation of the first dorsal interosseous (FDI) muscle. However, although not explicitly stated, it appeared that the reaction time was in fact the time to movement completion, rather than the onset of muscle activity. Our previous work has demonstrated that stimulus intensity has a profound effect on reaction time and that this difference may be represented cortically [21]. Furthermore, Bolton et al. [27] demonstrated significantly reduced hand muscle activity amplitude in both perturbation cued and auditory cued reach-to-grasp tasks following cTBS in the motor cortex contralateral to the targeted hand. Importantly, this work suggested that higher cortical centers, such as the M1 may be involved in both perturbation-evoked responses as well as auditory-cued responses and Pruszynski et al. [28] identified that processing through M1 can mediate sensory feedback for motor reactions. In the current study, the particular interest lies in the contribution of M1 to speeded sensorimotor transformations. Specifically, the primary objective is to explore the interaction between stimulus intensity and the effect of cTBS attenuation of M1 activity on simple reaction time and the amplitude of muscle activity. Based on our previous investigations, it is hypothesized that: (1) reaction time will be shorter following the high intensity stimulation compared to the low intensity stimulation in both limbs; (2) in the limb contralateral to the cTBS stimulated site, application of cTBS will result in an increased reaction time and relative reduction in muscle activity and this effect will be more pronounced following the high intensity stimulation compared to the low intensity stimulation; and (3) in the limb ipsilateral to the cTBS stimulated site, application of cTBS will result in a reduction of reaction time and facilitation of muscle activity and this effect will be more pronounced following high intensity stimulation compared to low intensity stimulation.

2. Methods

2.1. Participants

Thirteen healthy young adults (24 ± 5 years old; 9 males) with no history of musculoskeletal or neurological injury participated in this study. All participants provided informed consent, and the study received ethics clearance from the University of Waterloo's research ethics board.

2.2. Protocol

2.2.1. Task order

The layout of the protocol task order is presented in Fig. 1 and sections of the protocol are described in further detail below. Data collection was completed in the following order: (1) baseline TMS testing, including hotspot localization, determination of resting motor threshold, determination of active motor threshold and baseline MEP testing; (2) baseline behavioral testing; (3) cTBS delivery; (4) post cTBS MEP testing and (5) post cTBS behavioral testing.

2.2.2. Electromyography

Electromyography (EMG) was measured bilaterally from the 1st FDI, the prime mover for the behavioral task and motor cortical site of rTMS application, and abductor pollicis brevis, used to monitor the trial to trial amplitude of median nerve stimulation amplitude. EMG sites were cleaned with alcohol and abrasive cream, and shaved, if necessary. Silver/silver chloride electrodes were fixed 1 cm apart over each muscle belly. EMG signals were sampled at 1000 Hz, amplified by a magnitude of 1000, band-pass filtered online from 10 to 300 Hz (Noraxon, Scottsdale, AZ, USA), and stored for offline analysis. EMG signals were digitally filtered from 20 to 250 Hz (2nd order dual pass Butterworth) and conditioned by removing any DC offset bias and by full wave rectifying the signal. EMG onset latency (reaction time) was defined as the time when the EMG amplitude exceeded five standard deviations of the mean of a 100 ms baseline value taken prior to the median nerve stimulation. EMG amplitude was calculated for the FDI muscle as the total integrated EMG activity (iEMG) for 100 ms following