Theta-burst rTMS over SI modulates tactile perception on the hand

by
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A thesis
presented to the University of Waterloo
in fulfillment of the
thesis requirement for the degree of
Master of Science
in
Kinesiology

Waterloo, Ontario, Canada, 2011

Author's Declaration

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

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Abstract

Fine motor control of the hand relies on intact somatosensory integration and feedback. Impaired hand movements are observed in patient groups where touch perception and processing within the primary somatosensory cortex (SI) is abnormal. A repetitive transcranial magnetic stimulation paradigm called continuous theta-burst stimulation (cTBS) can be used to induce physiological changes to the underlying cortex. The effect of cTBS on tactile perception is unknown. This Master's research thesis examined the effect of cTBS over SI on tactile discrimination on the hand in healthy humans. Specifically, the goal of this thesis was to reveal the modulatory effects of cTBS on tactile temporal and spatial psychophysical measures on the hand. In separate experiments, temporal discrimination threshold (TDT) and the spatial measure of amplitude discrimination were measured from the right hand before and for up to 35 minutes following cTBS over left SI. Compared to pre cTBS values, TDT was elevated immediately following cTBS (3-6 minutes) and at later intervals (11-18 minutes). Spatial tactile perception was also measured through amplitude discrimination over the same time course and compared to pre cTBS values thresholds were impaired for up to 18 minutes. These experiments reveal that cTBS over SI impairs tactile acuity on the contralateral hand. The effects last for up to 18 minutes and subsequent measures return to pre cTBS levels. This work is important in identifying means to modulate SI cortical excitability and has potential for clinical application in patient groups with altered somatosensory processing.

Acknowledgements

I would like to thank all those people who have supported and contributed to my work here at the University of Waterloo.

First I'd like to thank my Masters supervisor, Dr. Aimee J. Nelson for her patience, support, advice, and much needed assistance. Thank you for your guidance during this process. Also a much appreciated thank you to the members of my committee: Dr. Bill McIlroy and Dr. Richard Staines for your feedback and constructive criticisms that helped strengthen my thesis work.

Thanks to all Neuroscience lab members, new and old, for their time, feedback, and words of encouragement along the way. A special thanks to Azra Premji for all her support in and out of the lab.

Lastly, and importantly, I want to thank my family and friends who have continued to offer me assistance despite not really knowing what my work truly involves. I wouldn't have been able to get to where I am in my life without your love and support. Thank you.

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List of Abbreviations

AMPA	Alpha (α)-Amino-3-hydroxy-5-Methyl-4- isoxazole-Propionic Acid
AMT	Active Motor Threshold
ANOVA	Analysis of Variance
CM	Cortical Metrics
CTBS	Continuous Theta-burst Stimulation
EMG	Electromyography
FDI	First Dorsal Interosseous
GABA	Gamma (γ)-Aminobutyric Acid
HFO	High-Frequency Oscillation
H-F	Huynh-Feldt
ISI	Interstimulus Interval
ITBS	Intermittent Theta-burst Stimulation
M1	Primary Motor Cortex
MEP	Motor Evoked Potential
msec	Milliseconds
MT	Motor Threshold
MVC	Maximum Voluntary Contraction
NMDA	N-Methyl-D-Aspartate
OIS	Optical Intrinsic Signal
RTMS	Repetitive Transcranial Magnetic Stimulation
SD	Standard Deviation
SEP	Somatosensory Evoked Potential
SI	Primary Somatosensory Cortex
TBS	Theta-burst Stimulation
TDT	Temporal Discrimination Threshold
TMS	Transcranial Magnetic Stimulation
μm	Micrometers
μV	Microvolts

Chapter 1: Goal of Thesis
Theta-burst rTMS over SI modulates tactile perception on the hand

1.1 Overview of Thesis

The goal of the Master's research thesis was to investigate the influence of continuous theta-burst repetitive transcranial magnetic stimulation (cTBS) over the primary somatosensory cortex (SI) on tactile perception on the hand. Selection of the hand as the site for study was based on the importance of normal hand function in daily activities. Healthy human adults typically have excellent tactile perception and accurate control of hand and finger movements that is regulated by the processing of somatosensory inputs (Mountcastle, 2005). Further, the large cortical representation of the hand within SI (Blake et al., 2002) improves the opportunity to modulate neural excitability within the hand region. The ability to modulate cortical processing within the touch cortex could identify paradigms that can alter tactile perception on the hand. Importantly, tactile psychophysical measures relate to physiological changes in cortical activity within SI and can therefore be used as an indicator of cortical function. The neural basis of tactile temporal and spatial psychophysical percepts on the hand is well understood and these exact measures have been obtained in several studies in healthy humans (Tannan et al., 2007a; 2007b; Tommerdahl et al., 2007; Francisco et al., 2008; Folger et al., 2008; Zhang et al., 2009) and patient groups for temporal discrimination (Lacruz et al., 1991; Artieda et al., 1992; Sanger et al., 2001; Bara-Jimenez et al., 2000; Fiorio et al., 2003; 2008; Lee et al., 2005; Tommedahl et al., 2008) and spatial tasks (Tannan et al., 2008). By examining any changes in these percepts in healthy individuals possible therapeutic modalities to alter touch perception in patient groups can be identified.

Repetitive transcranial magnetic stimulation (rTMS) applied over SI can modulate cortical excitability. Previous studies involving its application have shown modest impairments in tactile perception when applied at low-frequencies (Knecht et al., 2003; Satow et al., 2003; Morley et al., 2007; Hannula et al., 2008; Meehan et al., 2008; Vidoni et al., 2010) and improvements when applied at high-frequencies (Ragert et al., 2003; 2004; Tegenthoff et al., 2005; Pleger et al., 2006; Karim et al., 2006). Similarly, TBS facilitates (Katayama and Rothwell, 2007; Ragert et al., 2008, Premji et al., 2010) or suppresses (Ishikawa et al., 2007; Katayama et al., 2010) cortical activity depending on the type of stimulation applied. Generally the effects exhibited through the application of TBS are long lasting given the short duration and low intensity of the delivered stimuli allowing for an effective non-invasive technique for modifying cortical activity. However, there are currently no published studies that examine the use of cTBS to modulate spatial and temporal tactile acuity. This Master's thesis work encompasses novel experiments that have investigated the influence of cTBS on tactile perception on the hands. Measures of touch perception involved both temporal and spatial discrimination taken before and after cTBS.

1.2 Summary of Experiments

Experiment 1 investigated the modulation of tactile temporal discrimination on the hand following cTBS over SI. Measures of temporal discrimination thresholds were obtained in eight right-handed individuals before and following cTBS.

Experiment 2 investigated the modulation of tactile spatial discrimination on the hand following cTBS over SI. The spatial measure of amplitude discrimination thresholds were obtained in eight right-handed individuals preceding and following cTBS.

1.3 Significance of Master's Thesis Work

Experiments 1 and 2 provide novel neuroscience information on how tactile perception can be modulated following the application of cTBS over SI. Specifically, the results of both experiments reveal an impairment in tactile discrimination. This gives insight into not only the neural mechanisms involved in perception and TBS but also the ability to apply such methodology to patients that exhibit impaired motor control of the hand due to altered somatosensory processing.

1.4 Outline of Thesis Chapters

The experiments presented in this thesis were performed on healthy adults. The following chapter will review relevant literature and techniques used to conduct the two research experiments. Chapters 3 and 4 include detailed descriptions of the hypotheses, methods, and results from Experiments 1 and 2, respectively. A general discussion in Chapter 5 will summarize results from both experiments and provide an interpretation.

Chapter 2: Literature Review

2.1 Peripheral Encoding of Touch Stimuli

At the level of the dermis there are several types of cutaneous mechanoreceptors, which respond and act as the first afferent neuron to code for the stimulus properties. These receptors can be classified according to their subsequent ability to adapt to vibrotactile stimuli. Slowly adapting receptors (SA1) are Merkel's disks, which detect changes in pressure and have the smallest associated neural receptive fields. Rapidly adapting (RA) receptors are Meissner's corpuscles that detect light touch sensations while vibration is detected by Pacinian corpuscles (PC) that show larger receptive fields with increased stimulus amplitudes (Johnson et al., 2000). When a vibrotactile stimulus is applied all three receptor types are activated through generation of receptor potentials which then triggers action potentials within the respective nerve fiber allowing for the distinct encoding of the touch stimulus (Fromy et al., 2008). Further, somatosensory evoked potential (SEP) studies conducted on the hand have shown a particular range of modulated frequencies that result in temporal resonance with the highest signal to noise ratio notably being in the 21-26 Hz range (Tobimatsu et al., 1999).

2.2 Transmission of Afferent Input to SI

Once activation of cutaneous mechanoreceptors has occurred the afferent information is transmitted via the dorsal column medial leminiscus pathway to nuclei in the thalamus (Mountcastle, 2005). Specifically, the primary afferent extends from the cutaneous mechanoceptor and propagates its action potential up the axon towards its cell's body found in the respective dorsal root along the spinal cord. This primary afferent then extends along the dorsal column to pass through the fasciculus cuneatus and at the level of the caudal medulla

synapse with neurons in the nucleus cuneatus (Mountcastle, 2005). The secondary afferent

starting at the caudal medulla undergoes sensory decussation within the medulla and forms the

medial leminscus pathway in the rostal pons that extends along the brainstem and synapses with

neurons at the ventral posterolateral nucleus (VPL) in the thalamus (Mountcastle, 2005). Finally,

the third afferent extends from the thalamus to the specified region within the primary

somatosensory cortex. There is noted somatotopy throughout this pathway and within SI (Blake

et al., 2002; Hlustik et al., 2001) with respective receptive fields found within the cortex that are

activated by the vibrotactile stimulus reflecting the dynamic nature of SI (Lee and Whitsel,

1992).

2.3 Physiology of SI Neuronal Processing

2.3.1 Anatomical structure, input laminae, and columnar structure of SI

SI located in the postcentral gyrus bounded by the longitudinal lateral fissure, central, and

postcentral sulcus is commonly referred to as Brodmann areas 3a, 3b, 1 and 2 as defined by

Korbinian Brodmann from his cytoarchitectural studies in the early 1900s. Of those four

Brodmann areas, 3b and 1 mainly receive primary input from cutaneous afferents while 3a and 2

receive input from muscle spindles and joints (Mountcastle, 2005). From his work, six distinct

cortical layers with varying neuronal cell types were established with the most superficial mainly

consisting of apical dendrites of pyramidal neurons, lamina II-III containing the bulk of

pyramidal neurons and non-pyramidal intracortical axons including double-bouquet (DB) cells,

lamina IV mainly contains the stellate neurons, with layers V and VI containing large pyramidal

and multiform neurons (Mountcastle, 2005). The input from the VPL of the thalamus to SI

occurs within layers IV-VI (Whitsel et al., 1999; Thomson and Bannister, 2003) with stellate

cells propagating excitatory inputs through release of glutamate which act on the alpha (α)-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) receptors of the pyramidal cells of layers II and III as well as the DB cells. This results in the activation of the pyramidal neuron as well as the release of gamma (γ) -aminobutyric acid (GABA) from DB cells that inhibit both the basal dendrites of pyramidal cells and neighboring stellate neurons (Whitsel et al., 1999). Lateral inhibition results, which occurs along subunits of adjacent cortical columns, or minicolumns, that are vertically oriented linked neurons extending from layers II-VI of a mere 40-60 micron transverse diameter (Mountcastle, 2005). Studies have shown that neuronal cells that share the same minicolumn have similar receptive field properties (Tommerdahl et al., 2010) giving that receptive fields for SI neurons that occupy the same minicolumn are closer than the distinct skin sites would occupy different macrocolumns (a local collection of minicolumns). Several studies have used this neurophysiology of SI to determine the how various aspects of vibrotactile stimuli are coded.

2.3.2 SI encoding of peripheral stimuli within area 3b

Stimulus coding has been examined at the cortical level within SI from the results of optical intrinsic signal (OIS) studies on squirrel monkeys, which are an indirect reflection of neuronal activity in the observed cortex. A study by Chen et al. (2001) revealed the topographic organization of the hand and cortical representation of pressure, flutter, and vibration of area 3b after stimulus application to the hand. The activations showed minimal overlap between adjacent skin sites and distinct topography that was maintained across varying vibrotactile frequencies (Chen et al., 2001). Functional magnetic resonance imaging (FMRI) studies have confirmed this topographical hand representation (Chen et al., 2007) giving similar maps obtained from OIS studies (Chen et al., 2003).

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2.3.3 Amplitude and temporal encoding

It was determined that with an increase in amplitude of the stimulus the spatial extent of the response in the SI cortex remained the same while the same cortical region does increase the magnitude of neuronal response proportional to the intensity of firing (Simons et al., 2005). Increasing duration evokes increasingly higher absorbance within the central cortical region (Simons et al., 2007) with less absorbance in the surround – indicative of increasing lateral inhibition that is amplitude and duration dependent. Further, the OIS persists for longer durations with increased duration of stimulus. The application of two simultaneous stimuli of a set amplitude and duration on the hand within adjacent receptive fields results in surround inhibition within SI, which is a decrease in the area and amplitude of cortical neuronal activation between receptive fields (Friedman et al., 2008; Chen et al., 2003). Temporally separating these stimuli can further impair detection due to in-field inhibition within SI, due to neuronal suppression within the receptive field itself resulting in a subsequent decrease in neuronal firing (Gardner and Costanzo, 1980; Laskin and Spencer, 1979).

2.4 Cortical Metrics Device (CM)

The Cortical Metrics device is a dual-site vibrotactile stimulator that can be used to obtain psychophysical measures on the hands. The two independently controlled probes allow simultaneous or sequential stimuli delivery to two skin sites (horizontal range from 0 to 60 mm apart) with varying amplitude, frequency, or duration (Tannan et al., 2007a). Using a LabVIEW (v 8.5 National Instruments Corporation, Texas USA) designed interface and programming, the device allows for manipulation of both the vertical and horizontal positioning of the probes as well as application of designed protocols to obtain psychophysical measures. This device has

been used in several studies on control (Tannan et al., 2007a; 2007b; Tommerdahl et al., 2007; Folger et al., 2008; Francisco et al., 2008; Zhang et al., 2009) and three studies involving patient groups (Tannan et al., 2008; Folger et al., 2008; Tommerdahl et al., 2008). See Figure 2.1 for device and Tannan et al. (2007a) for full description. Several protocols have been established to test for temporal and spatial acuity using the CM device allowing for a reliable means to assess mechanisms involved in tactile perception on the hands. Touch perceptual measures are defined as being those mediated by variations in cutaneous stimulation while tactile discrimination involves the interpretation and integration of the spatial and temporal aspects of touch. To assess touch perception measures of tactile discrimination were obtained using the CM device.

Figure 2.1: Cortical Metrics device pictured alone and pictured with a subject's hand dorsum under probes.

2.4.1 Temporal discrimination threshold (TDT)

This protocol involves the application of two probes that vibrate at a set frequency with constant indentation for a short duration with an initial interstimulus interval (ISI) that set and is

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adjusted according to the subject response to whether they felt the probes vibrate at the same time on their hand. A correct response results in the lowering of the ISI by a set interval while an incorrect response increases the ISI by the same value. The measure of temporal discrimination threshold has been used in healthy subjects (Tommerdahl et al., 2007) and patient populations (Tommerdahl et al., 2008).

2.4.2 Amplitude discrimination

This protocol involves the application of two probes that vibrate simultaneously for a set time period at a constant frequency with one probe (the *standard*) set at a lower indentation than the other probe (the *test*). Following the vibration, the subject is queried to respond through a mouse click, which probe site they perceived as more intense. For correct responses, stimulus intensity of the test probe was lowered for the following trial at a set increment (i.e. making the task more difficult). An incorrect response would result in an increase in the stimulus intensity of the test probe (i.e. making the task easier). The spatial measure of amplitude discrimination has been used in healthy subjects (Tannan et al., 2007a; 2007b; Folger et al., 2008; Francisco et al., 2008; Zhang et al., 2009) and patient populations (Tannan et al., 2008).

2.5 Transcranial Magnetic Stimulation (TMS)

2.5.1 Mechanisms

Transcranial magnetic stimulation (TMS) is a non-invasive method of stimulating cortical neurons and examining their circuits in humans based on the principle of electromagnetic induction of an electric field in the brain. According to Michael Faraday's law of electromagnetic induction a magnetic field induces an electrical field which when applied as TMS is proportional and determined by the rate of change of current in the coil (Rossi et al.,

2009). This magnetic field can reach up to 2 Tesla and lasts for about 100 microseconds (Hallet, 2007). The focus of the magnetic field depends on the shape of the coil, for example the commonly used figure of eight coil produces a more focal and shallow stimulation at a depth of 1.5-3.0 cm beneath the scalp depending on the stimulation intensity (Rossi et al., 2009). As the coil is placed over the scalp the induced electric field results in ion flow in the brain and can generate an action potential if sufficient intensity of stimulation is used. When this occurs over the primary motor cortex (M1) the descending volleys can be produced in the corticospinal pathway resulting in muscle activation that can be recorded by surface electromyography (EMG) (Edwards et al., 2008). Several forms of TMS can be applied to the scalp and used to assess and change cortical neuron excitability.

2.5.2 Single-pulse TMS

Single-pulse TMS when applied over M1 can result in a motor evoked potential (MEP) that can be measured through EMG on the contralateral muscle. A commonly used muscle includes the first dorsal interosseous muscle (FDI) however other muscles of the hand and forearm can be used. Correctly determining the site of the motor hotspot of a muscle depends on coil orientation and stimulus intensity (Kobayashi and Pascual-Leone, 2003). Active motor threshold (AMT) is the lowest intensity required to elicit MEPs that are 200 microvolts or greater in amplitude for 5 out of 10 consecutive trials during 10% maximum voluntary contraction (MVC) (Orth and Rothwell, 2009). The purpose of determining these motor thresholds (MT) is to select the appropriate stimulation intensity to be used for forms of repetitive TMS.

2.5.3 Repetitive TMS (rTMS) and Theta-burst stimulation (TBS)

RTMS is a form of TMS that applies trains of multiple stimuli to the same cortical area that has been shown to alter cortical excitability. When rTMS is applied at a high-frequency with short stimulation duration and intensity it can induce changes in cortical excitability that outlast the period of stimulation for up to 60 minutes (Huang et al., 2005). This form of rTMS known as theta-burst stimulation (TBS) may be applied continuously (cTBS) or intermittently (iTBS) over SI to induce physiological and perceptual changes. Protocols introduced by Huang and colleagues use a general TBS pattern that applies 3 pulses of stimulation at 50 Hz repeated every 200 msec (Huang et al., 2005) (see Figure 2.2). At present the mechanisms of action of TBS are not fully understood. Two possible mechanisms for the influence of TBS include a role of *N*-methyl-D-aspartate (NMDA) and GABA receptors (Cardenas-Morales et al., 2010). Few studies have examined the effect of rTMS and TBS over SI.

2.5.4 TBS over SI

iTBS

The application of iTBS over SI leads to an increase in somatosensory evoked potentials (SEP) indicating cortical facilitation that lasts at least 25 minutes post stimulation (Katayama et al., 2007; 2010; Ragert et al., 2008; Premji et al., 2010). Further, in one study a concomitant improvement in tactile perception on the hand was observed for up to 30 minutes (Ragert et al., 2008). Other studies that have applied iTBS over SI have also shown suppression in the amplitude of laser-evoked potentials (Poreisz et al., 2008) and hemoglobin concentration (Mochizuki et al., 2007) giving that the effect of this paradigm can be variable over the same non-motor cortical region.
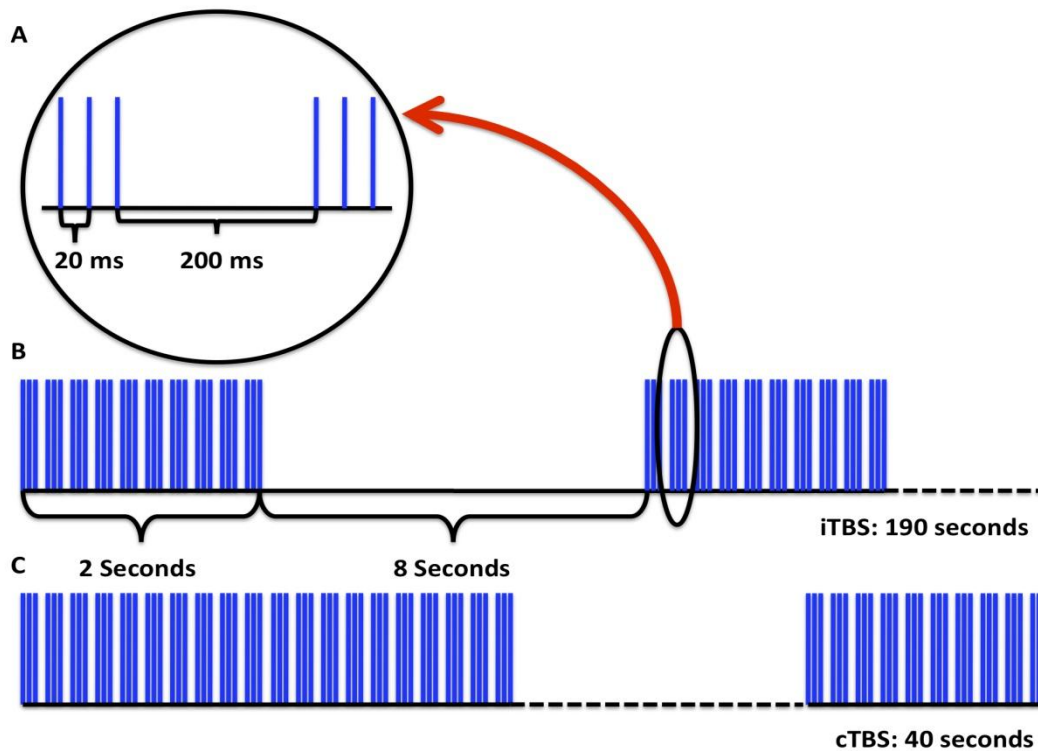
Figure 2.2: General theta-burst stimulation (TBS) pattern with three pulses of stimulation given at 50 Hz repeated every 200 msec (A). Intermittent TBS (iTBS) pattern with a 2 second train of TBS repeated every 10 seconds for a total of 600 pulses (B). Continuous TBS (cTBS) pattern with a total of 600 pulses delivered over 40 seconds (C). Figure adapted from Huang et al., 2005.

cTBS

TBS when applied continuously (cTBS) over SI leads to a subsequent decrease in SEPs indicating cortical suppression that lasts about 13 minutes post stimulation (Ishikawa et al., 2007). Further, cTBS suppresses the late component of high-frequency oscillations (HFO) which are thought to reflect actions of inhibitory interneurons within SI (Katayama et al., 2010). The effect of this paradigm tends to suppress cortical activity within SI also revealed through changes in the amplitude of laser-evoked potentials (Poreisz et al., 2008) and hemoglobin concentration (Mochizuki et al., 2007).

Chapter 3: Experiment 1
Modulation of tactile temporal discrimination on the hand following continuous theta-burst stimulation over the primary somatosensory cortex

3.1 Introduction

Fine motor control of the hand relies on cutaneous input originating from skin contact surfaces (Johnson et al., 2000), the integrity of afferent transmission (Marino et al., 1999), and processing within primary and higher order somatosensory loci (Mountcastle, 2005). Impaired hand movements are observed in patient groups such as focal hand dystonia whereby touch perception and processing with somatosensory cortex is abnormal (Tinazzi et al., 2009; Bara-Jimenez et al., 1998; Abbruzzese and Berardelli, 2003; Lin and Hallett, 2009). Similarly, impaired hand control and severe deficits in touch perception may occur subsequent to stroke (Castillo et al., 2008; Carey, 1995). To date, sensory stimulation rehabilitation experiments that attempt to alter touch perception have resulted in short-lasting and modest improvements in sensation and hand function (Zeuner et al., 2002; 2003; Yekutiel and Guttman, 1993; Carey et al., 1993; 2005; Smania et al., 2003). One component of altering touch perception involves suppressing sensory input that is irrelevant or distracting, impairments in such occurs in patients with autism spectrum disorder (ASD) and cerebral palsy (CP) (Cascio, 2010). Therefore, identifying approaches that can modify touch perception may potentially lead to therapeutic regimes that can assist in patients with impaired hand control.

One method that can alter perception is through the application of repetitive transcranial magnetic stimulation (rTMS). RTMS applied over primary somatosensory cortex (SI) modifies tactile perception (Tegenthoff et al., 2005, Ragert et al., 2003, Pleger et al., 2006, Karim et al., 2006) and cortical physiology (Pleger et al., 2006, Tegenthoff et al., 2005, Ragert et al., 2004).

RTMS approaches may alter touch perception and symptoms of impaired hand control in patient groups (Dystonia: Borich et al., 2009; Schneider et al., 2010, Stroke: Nowak et al., 2008; Dafotakis et al., 2008). One particular form of rTMS, known as theta-burst repetitive TMS (TBS), involves low-intensity short duration pulses that yield effects for up to one hour post stimulation (Huang et al., 2005). TBS may be applied continuously (cTBS) or intermittently (iTBS) over SI to induce physiological and perceptual changes. CTBS applied over SI suppresses somatosensory evoked potentials (SEPs) for 13 minutes (Ishikawa et al., 2007) though the effects on tactile perception are unknown. ITBS to SI increases SEP amplitudes for at least 25 minutes post stimulation (Katayama et al., 2007; 2010; Premji et al., 2010) however the effects of this TBS paradigm are more variable over SI (Poreisz et al., 2008; Mochizuki et al., 2007) and other non-motor areas (Franca et al., 2006; Koch et al., 2007) than those observed with cTBS application. One study demonstrated that tactile spatial acuity improves immediately following iTBS over SI (Ragert et al., 2008).

Temporal discrimination threshold (TDT) is a measure of tactile acuity defined as the shortest time interval whereby two sequential stimuli are perceived as distinct (Tommerdahl et al., 2007). In healthy humans TDT on the hand ranges from 20-50 msec (Tommerdahl et al., 2007; Hoshiyama et al., 2004; Pastor et al., 2004; Lacruz et al., 1991) with certain patient groups having values outside this control range (Lacruz et al., 1991; Sanger et al., 2001; Bara-Jimenez et al., 2000; Fiorio et al., 2003; 2008; Artieda et al., 1992; Tommerdahl et al., 2008). Abnormal TDT values suggest deficiencies in cortical function that may contribute to the pathophysiology of motor deficits. It remains unknown whether touch perception in the time domain may be altered by TBS. However, if TDT can be altered by TBS paradigms this will provide information about how to use TBS to alter touch perception in clinical populations.

The present study investigated the influence of cTBS over left SI on TDT from the right hand. The cTBS paradigm was applied to examine the modulation in temporal tactile perception and will provide novel neuroscience information. It was hypothesized that cTBS would increase TDT such that tactile perception would be impaired compared to pre cTBS values for up to 13 minutes post stimulation in line with the duration of physiological effects (Ishikawa et al., 2007; Katayama et al., 2010).

3.2 Methods

3.2.1 Participants

Eight subjects (4 females, mean age 29 years ± standard deviation (SD) 5.1 years) participated. Right-handedness was determined using a subset of the Edinburgh Handedness Inventory (EHI) (Oldfield, 1971). All subjects were required to give informed written consent prior to study participation. The study was approved by the Office of Research Ethics at the University of Waterloo and conformed to the Declaration of Helsinki.

3.2.2 Experimental approach

Electromyography (EMG) Recording

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

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 (conducted on a 3T GE scanner obtaining 172 images with 3DFSPGR-IR sequences using a 20 cm FOV) with the coil to determine and monitor the accuracy of coil placement. To determine the intensity of cTBS, the motor hotspot was identified and the active motor threshold (AMT) was determined from this location. The motor hotspot was defined as the location within the primary motor cortex (M1) that elicited a motor evoked potential (MEP) in the contralateral FDI muscle with the coil oriented 45 degrees to the mid-sagittal line. AMT was defined as the lowest intensity required to evoke MEPs of 200 µV amplitude or greater in 5 out of 10 consecutive trials (Orth and Rothwell, 2009). For AMT participants were instructed to abduct FDI in a maximum voluntary contraction (MVC) against the base of the Brainsight apparatus. The EMG signal was displayed on an oscilloscope and the position of the line representing the FDI contraction was adjusted to 10% of their MVC. CTBS was applied at 80% AMT over SI defined as a point 2 cm posterior to the motor hotspot (Okamoto et al., 2004) with the handle oriented backward and laterally at a 45 degree angle away from midline (Ragert et al., 2008). See Figure 3.1 for an example of the cTBS coil location in one participant.
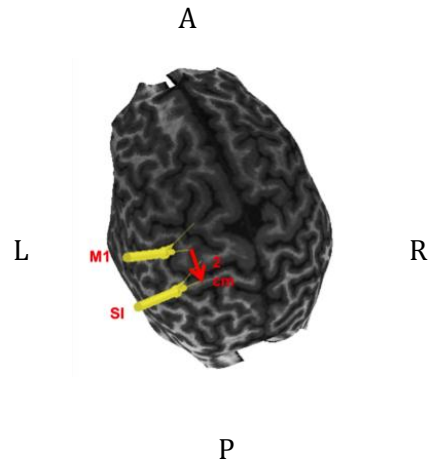
Figure 3.1: An example of TBS coil location for one subject that was determined using Brainsight Neuronavigation software. The motor hotspot for subject's left first dorsal interosseous shown (as M1) and SI identified as 2 cm posterior (Okatmoto et al., 2004).

Psychophysical Task

Using the Cortical Metrics (CM) device (Tannan et al., 2007a) TDT measures were collected immediately preceding cTBS and at six time blocks following: 3-6, 7-10, 11-14, 15-18, 23-26, and 31-34 minutes. All psychophysical measures were conducted in a quiet room with the subject seated at a table with a laptop monitor positioned in the center, the CM device to the side, and a computer mouse for response selection on the opposite side as the CM device. The hand dorsum was selected as the site of experimental measure to reduce any issues related to innervation across the skin region and any between-subject use dependent changes in sensitivity on the hands (Tannan et al., 2007a). Subjects placed their dorsum of their right hand under the device opening to allow the plastic probes of the device to lower until a registered force of 0.1 g. The CM device then further indented the two probes by 500 microns to ensure skin contact prior to stimulation onset. The interprobe distance was set at 32 mm and remained constant throughout. All CM protocols were run through programs designed with LabView (v 8.5, National Instruments Corporation, Texas, USA).

Training Trials

At the start of the experiment three sets of training trials for the TDT task were performed. Training trials were included to familiarize subjects with the task before commencing the testing trials. Training trials were performed in three blocks to ensure subjects had an ample number of trials to learn the task and so trends across these training trials could be later examined. Each block required participants to perform the TDT task and obtain 5 correct consecutive responses. During the training trials, subjects indicated their readiness to begin by making a mouse click. The ISI values used for training were between 5 and 60 msec. During training trials visual feedback was given via the laptop monitor and indicated to participants whether their response was correct (happy face, 'good job!') or incorrect ('please try again').

Test Trials

Following the training trials, the location of the probes on the right hand dorsum was marked to aid in alignment of the probes to the same skin site for subsequent trials. The first block of test trials began immediately following the training. For each test block subjects indicated their readiness by making a mouse click. For each trial, the two probes were vibrated for 40 msec with an amplitude of 200 microns of indentation and at a frequency of 25 Hz. In each block, the very first trial imposed an interstimulus interval (ISI) of 60 msec between the first and second vibrating probes. Subjects were queried to report whether they felt the two probes vibrate at the same time. Subjects responded by selecting the appropriate mouse click (left for yes, same time, right otherwise). The accuracy of the participants' response determined the adjustment of the ISI for the following trial. The ISI was adjusted by 5 msec on 1 up/1 down response for the first 10 trials and 2 up/1 down for the last 10 (two correct responses decreased the ISI by 5 seconds while one incorrect response increased the ISI by 5 seconds). Therefore, a

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correct response resulted in the ISI decreasing by 5 msec. The adjustment from the 1 up/1 down

to a 2 up/1 down protocol was used as it has been previously shown this allows for a reliable and

accelerated means to obtain threshold values (Tannan et al., 2007a; Tommerdahl et al., 2007).

Trials were separated by a minimum of 5 seconds and subjects were prompted by visual cues

displayed on the laptop monitor in advance of the next trial. Each block consisted of 20 trials

collected over 2.5 minutes. Auditory cues were minimized by the use of earplugs during training

and test trials. Further, all training and testing trials were video-recorded for quality assurance

purposes. A schematic of the TDT task is shown in Figure 3.2.
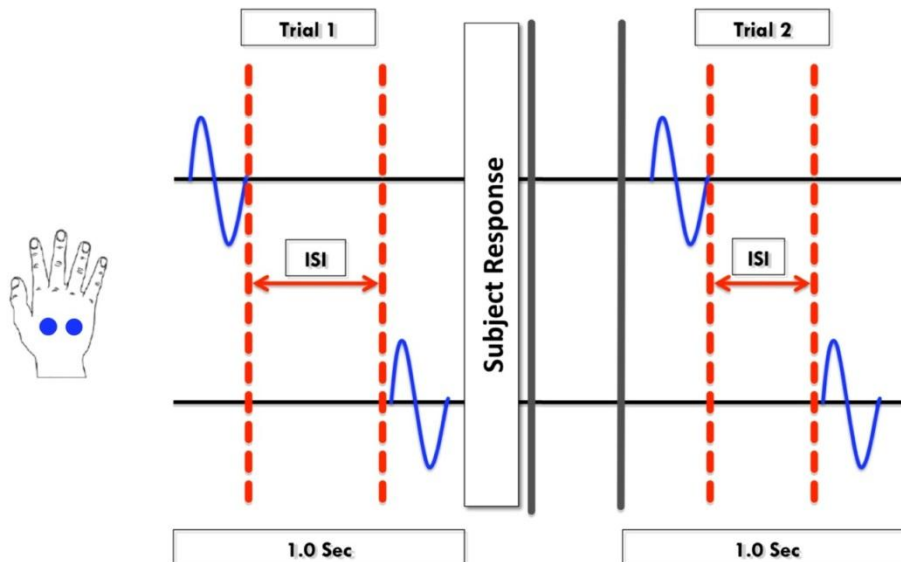
Figure 3.2: The temporal discrimination threshold (TDT) task. Two trials are shown with
correct subject response resulting in lowering of the ISI by a set increment of 5 msec.

3.2.3 Data analysis

The TDT thresholds obtained from the last five trials (trials 16 to 20) for each TDT

measure were averaged to obtain each subjects threshold for the psychophysical task

(Tommedahl et al., 2007; 2008). Figure 3.3 displays an example of a testing trial for one

participant.

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Figure 3.3: Temporal discrimination threshold. A sample of one subject's testing trials for this task is given. To establish each subject's threshold the average of the last 5 trials was calculated (Tommerdahl et al., 2007), shown above as a red dashed line.

For the training trials, the total number of trials performed by an individual to successfully complete each of the three training blocks was summed. As described earlier, five correct and consecutive responses were required to end a block of training trials. The number of trials for each block was averaged for the group and p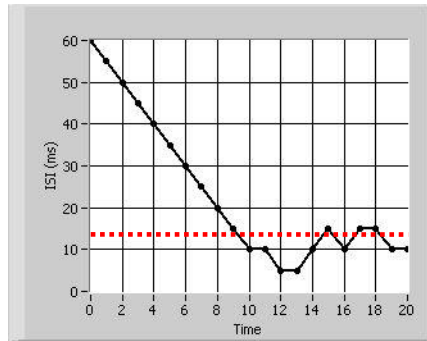lotted. To determine any improvements in performance across the blocks a Friedman test with Bonferroni corrected contrasts (corrected for three comparisons, block 1 versus block 2, block 1 versus block 3, and block 2 versus block 3) was conducted to compare performances between the first and subsequent training blocks. Statistical significance was set at $p \leq 0.05$.

One-way repeated measure analysis of variance (ANOVA) with within-subject factor 'TIME' (7 levels; pre, post 1, post 2, post 3, post 4, post 5, post 6) was performed for the testing trials. A priori hypotheses were tested using contrast estimations and Bonferroni correction (corrected for 3 comparisons, pre cTBS versus post 1, pre cTBS versus post 2, and pre cTBS versus post 3). To correct and test for sphericity, the Huynh-Feldt (H-F) estimate was used as a correction factor where necessary to reveal whether the data violated the assumptions of ANOVA. Post-hoc analysis was performed using Dunnett's test to test for any other differences

following cTBS application. All statistical analysis was performed using SAS 9.2 Windows

software (SAS Institute Inc., Cary, North Carolina, US). Significance was set at $p \leq 0.05$.

3.3 Results

All participants successfully completed the experiment. The mean active motor threshold

(AMT) for the tested participants was 48 ± 10.8 % of the stimulator output with cTBS being

delivered at $38 \pm 8.5\%$.

3.3.1 Training trials

All subjects completed three blocks of training. The group-averaged means (with

standard errors) for the training trial blocks are shown in Figure 3.4. The y-axis plots the total

number of trials performed to reach the criteria of 5 correct consecutive responses. All subjects

showed improvement in their ability to perform the task and were able to complete the last

training block in fewer trials than required for block 1 and block 2. By Block 3 only 6 ± 1.5

(SD) trials were required before reaching the performance criteria. These data suggest that

subjects understood the task instructions and were able to perform the task correctly. Friedman

test showed no significant main effect of BLOCK ($F_{(2,7)} = 3.37$, $p = 0.0638$). A priori contrasts

revealed a significantly lower number of TDT training trials for the third block compared to the

first block ($p = 0.0245$). However, following Bonferroni correction (for three contrasts) this

difference remains insignificant.

Training Trials:
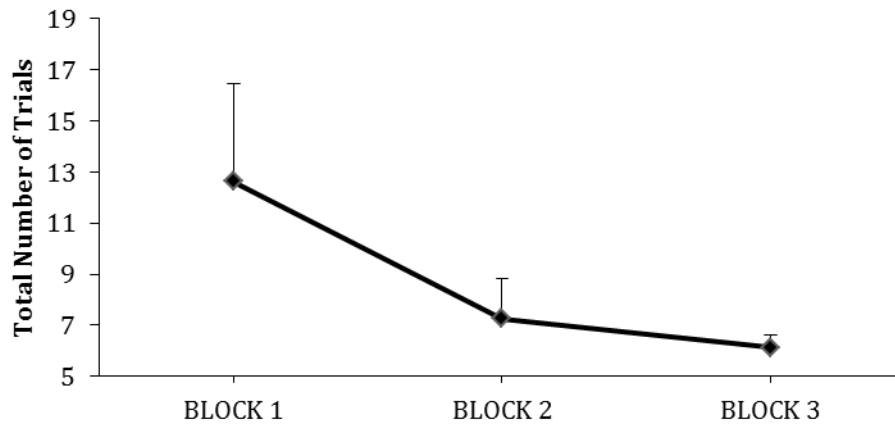## Temporal Discrimination Threshold

Figure 3.4: Results from training trials for the temporal discrimination threshold task (N = 8). Subjects were required to complete three blocks of training with five correct responses required to complete a block. Total number of trials is reported.

3.3.2 Test trials

The pre cTBS TDT values measured from the last five trials for the eight subjects tested was 26 ± 12 msec (SD). The ANOVA revealed a significant main effect of TIME ($F_{(6, 42)} = 5.40$, $p = 0.0003$, H-F $p = 0.0004$). A priori contrasts revealed that TDT was significantly greater at post 1 (3-6 minutes, $p = 0.0003$) and post 3 (11-14 minutes, $p = 0.0273$) blocks compared to pre TBS. Dunnett's post hoc analysis further revealed that TDT thresholds were significantly greater at post 4 (15-18 minutes) compared to pre cTBS values ($p \leq 0.05$). Figure 3.5 displays the group-averaged TDT (with standard error) at each time block tested. Table 3.1 displays the total number of participants who demonstrate the impairment in TDT at the post 1, 3, and 4 time blocks.

The impairment in temporal tactile perception was not observed at post 2 (7-10 minutes) as hypothesized. To further examine whether the effects could be seen at post 2, additional analysis was conducted to examine TDT values from other trials in addition to the last 5 (trials

16-20), specifically for trials 11 to 15. Figure 3.6 plots the group-averaged temporal discrimination threshold (with SD) for each test trial. One-way ANOVA revealed a significant main effect of TIME ($F_{(6, 42)} = 4.02$, $p = 0.0029$, H-F $p = 0.0029$). Figure 3.7 displays the group-averaged TDT (with standard error) for trials 11 through 15 at each time block tested. A priori contrasts revealed that TDT was significantly greater at post 1 (3-6 minutes, $p = 0.0011$) and post 3 (11-14 minutes, $p = 0.0017$) blocks compared to pre TBS.

Temporal Discrimination Threshold
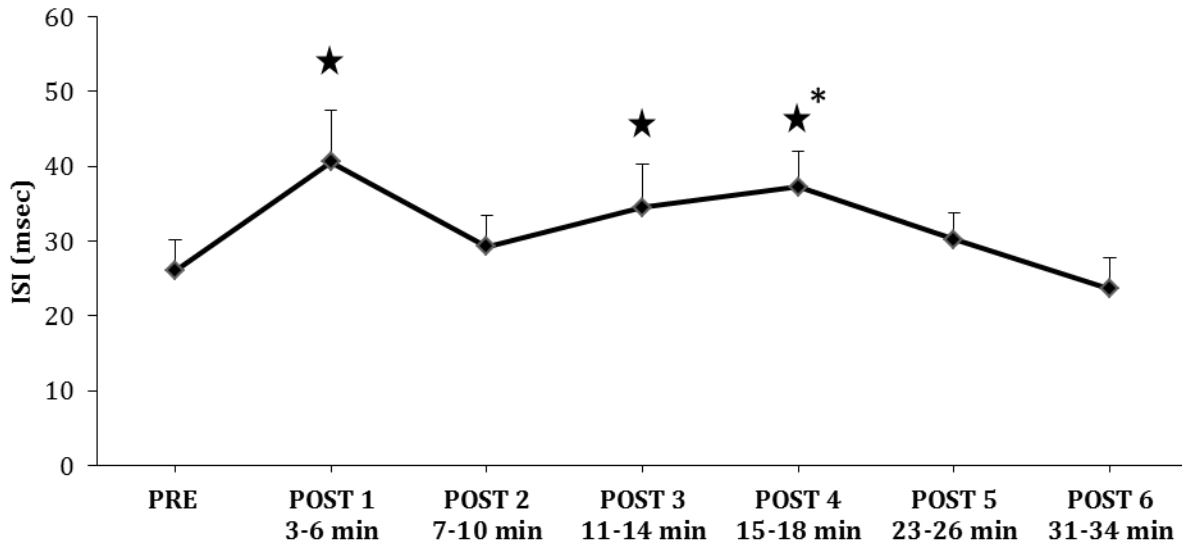
Figure 3.5: Results from the last five testing trials for the temporal discrimination threshold task (N = 8). TDT values were elevated post 1 (p = 0.0003), post 3 (p = 0.0273) and at post 4 (*Dunnett's, $p \leq 0.05$). Asterisks above the time interval note statistical significance. Error bars represent standard error of the means.

Temporal Discrimination Threshold (N = 8)

	Post 1	Post 3	Post 4
Increase	7	5	7
Decrease	1	2	1
No Change	0	1	0

Table 3.1: Summary of trends noted at post 1, post 3, and post 4 for all subjects tested compared to pre cTBS threshold values for the last five trials in the temporal discrimination threshold task.

Temporal Discrimination Threshold
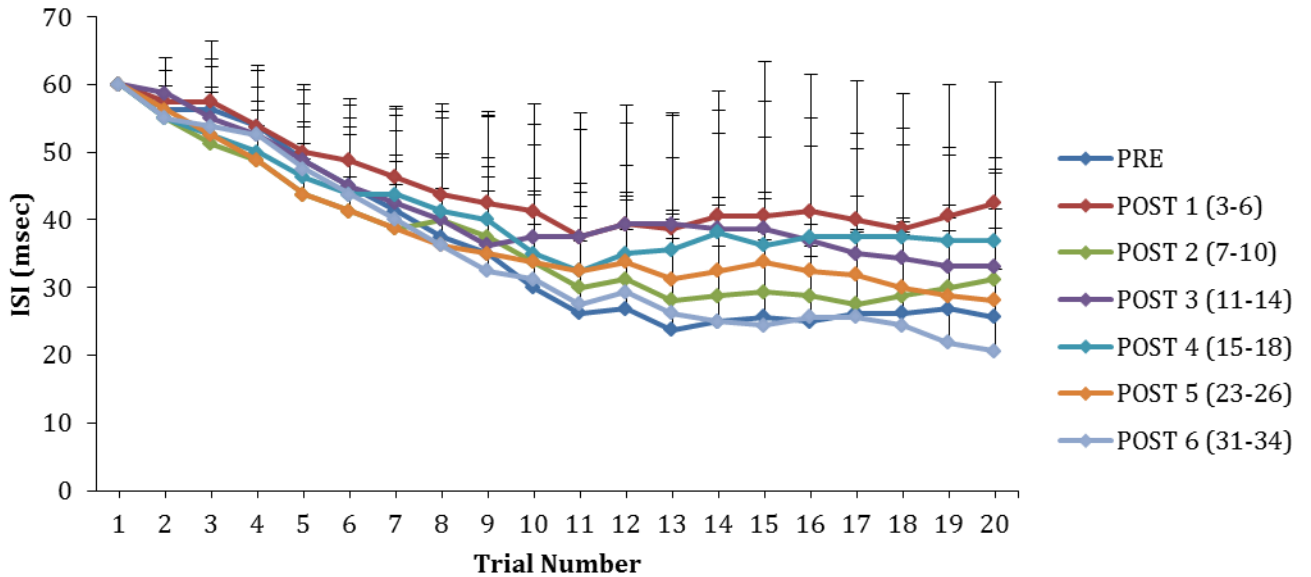
Figure 3.6: Results from all testing trials for the temporal discrimination threshold task (N = 8). Error bars represent standard deviation.

Temporal Discrimination Threshold

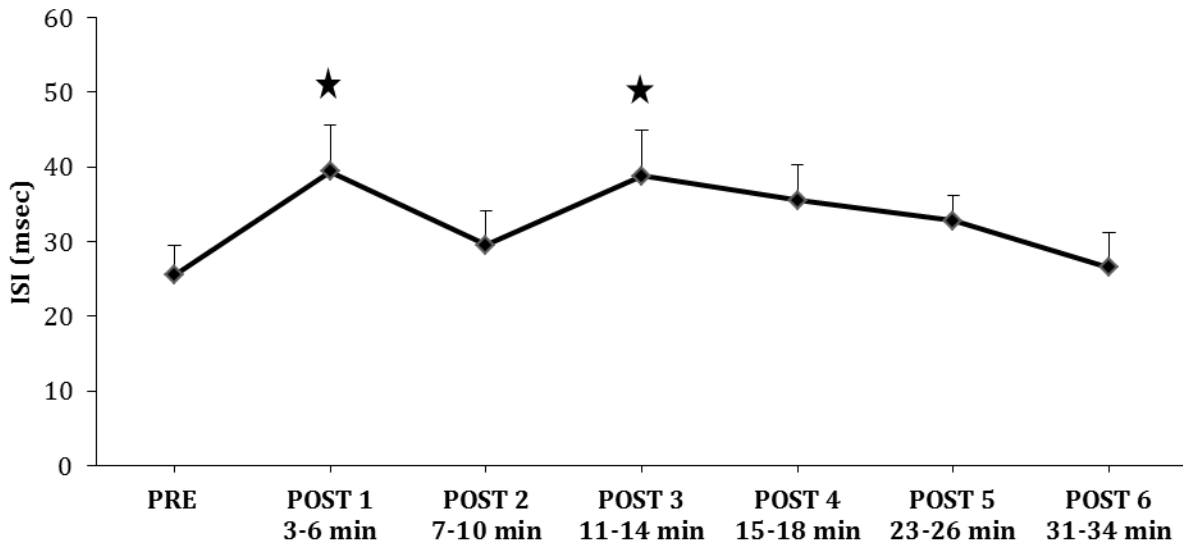**Figure 3.7:** Results from testing trials 11-15 for the temporal discrimination threshold task at each time interval for all subjects (N = 8). TDT values were elevated post 1 (p = 0.0011), post 3 (p = 0.0017). Asterisks above the time interval note statistical significance. Error bars represent standard error of the means.

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3.4 Discussion

The present experiment investigated the effect of cTBS over left SI on temporal tactile acuity on the dorsum of the right hand. This study revealed that TDT is impaired and thresholds are elevated following cTBS application at specific time intervals for up to 18 minutes. The observed changes in perception align with physiological data such that SEPs are depressed for up to 13 minutes following cTBS over SI (Ishikawa et al., 2007). However, the duration of the perceptual after-effects persist longer than physiological changes (Ishikawa et al., 2007; Katayama et al., 2010) and suggests that there may be several mechanisms imposing the changes in cortical excitability within SI. Potential mechanisms and the changes observed in temporal threshold are discussed in the following paragraphs.

Following cTBS, participants found it more difficult to discern the two temporally separated stimuli at specific time blocks. The neural basis considered to underlie temporal discrimination is derived from electrophysiology and optical imaging studies in monkeys. Simultaneous stimuli with the same amplitude and duration applied to the hand within adjacent receptive fields results in surround inhibition within SI, which is a decrease in the area and amplitude of cortical neuronal activation between receptive fields as compared to single site stimulation (Friedman et al., 2008; Chen et al., 2003). Temporally separating these stimuli can further alter detection due to inhibition within the receptive field itself resulting in a subsequent decrease in neuronal firing, this is known as in-field inhibition (Gardner and Costanzo, 1980; Laskin and Spencer, 1979). This inhibition hinders detection of a test stimulus when that stimulus is applied within a short interstimulus interval (ISI) after the conditioning stimulus. Complete suppression of the test stimulus has been seen with an ISI less than 40 msec when both stimuli are applied over the same receptive field while applying the test stimuli to an adjacent

site results in less suppression with return to control values by 60 msec (Gardner and Costanzo,1980). Specifically with electrical stimulation, it has been shown that ISI values from 3-30 msec can be perceived as a single test stimulus with subjects requiring ISI values of 50 msec to consistently detect the two stimuli as being sequential and clearly separated (McComas and Cupido, 1999).

Before cTBS, TDT values were 26 ± 12 msec (SD) and within the range as reported elsewhere (Tommerdahl et al., 2007; Hoshiyama et al., 2004; Pastor et al., 2004; Lacruz et al., 1991). Following cTBS, elevated thresholds were still within the range of control data but showed significant impairment compared to pre cTBS values. Specifically, TDT threshold values in msec with percent change from pre cTBS values were 40.6 (56% increase), 34.5 (33% increase), and 37.3 (44% increase) for post 1, 3, and 4 time blocks, respectively. Similarly, patients with focal brain lesions within SI or subcortical structures such as the basal ganglia show an elevated TDT on the hand contralateral to the affected hemisphere with a mean threshold value of 172.8 msec (Lacruz et al., 1991). Elevated TDT are also seen in patients with focal hand dystonia with threshold values ranging from 95-155 msec (Sanger et al., 2001; Bara-Jimenez et al., 2000; Fiorio et al., 2003), from 78-95.2 msec in Parkinson's disease (Fiorio et al., 2008; Artieda et al., 1992) and 37 msec in autism patients (Tommerdahl et al., 2008). The results of this experiment suggest that while there is an induced impairment in TDT following cTBS application, this modulation in tactile perception is not as severe as those seen in patient groups.

Examining the associated cortical and subcortical impairments for these clinical groups can reveal associations between how cTBS results in elevated TDT values and further understanding the cause of abnormal sensory processing. Specifically in the case of focal hand

dystonia (FHD), somatosensory abnormalities within SI have been shown to result in suppression of afferent-input gating (Frasson et al., 2001) demonstrated by increased paired-pulse SEP amplitude, which revealed a loss of inhibitory mechanisms within SI (Tamura et al., 2008). This result was associated with the levels of GABA, specifically the deficiencies that decrease the surround inhibition and can result in elevated TDT values since sensory gating is essential for the spatial and temporal separation of stimuli (Tamura et al., 2008). With autistic patients, elevated TDT values have been attributed to dysfunctional connectivity within SI cortical regions with specific loss of neutrophil surrounding minicolumns, which contain the inhibitory double- bouquet cells (Casanova et al., 2006). Thus, this loss in the GABA-mediated inhibition between these minicolumns could account for elevation in TDT in the patient group compared to control values (Tommerdahl et al., 2008). The values of TDT obtained in this study following cTBS application are comparable to those measured in subjects with autism. It is possible that cTBS acts on the inhibitory interneurons within SI. Cortical imaging studies have shown that cTBS activates GABA interneurons within the cortex (Stagg et al., 2009) that can be related to its ability to modify synaptic inputs through inhibitory interneurons (Benali et al., 2011).

Previous applications of cTBS over SI have investigated the modulation of SEPs and results of this experiment are in line with the direction of effects exhibited, with there being suppression of tactile perception. Examination of SEP components can reveal how cortical and subcortical regions within SI cortex respond to TBS. In particular the amplitude of P25/N33 cortical potentials were suppressed following cTBS over SI for 13 minutes as measured by two time blocks at 0-3 and 10-13 minutes with no significant suppression noted at 20 minutes (Ishikawa et al., 2007). In the present study TDT values were elevated from 3-6 (post 1) and 11-

14 (post 3) minutes as hypothesized based on the physiological results but were unchanged from 7-10 minutes (post 2), a time range yet to be explored using SEPs. Further, the continued elevation in TDT values from 15-18 minutes (post 4) is incongruent with a recent study by Katayama et al. (2010) that did not reveal any SEP changes at 15 minutes following cTBS application. However, this study did reveal that cTBS suppressed late high-frequency oscillations (HFO) at 15 minutes following stimulation (Katayama et al., 2010). The late subcomponent of HFOs are said to represent GABAergic inhibitory interneurons within layer 4 of SI (Hasimoto et al., 1996) and possibly involve cholinergic transmission between pyramidal neurons (Restuccia et al., 2003) while cortical SEPs are considered to be generated by excitatory postsynaptic potentials of the apical dendrites of pyramidal neurons (Allison et al., 1991). It is possible that differing mechanisms are mediating the changes in TDT at these intervals and examination of the cortical mechanisms behind physiological measures can assist in explaining the effects on psychophysics.

Clinically, the impairment of tactile perception seen by cTBS over SI may aid in regulating relevant cortical processing within SI. Just as important as modulating touch perception of task-relevant information is the ability to apply sensory gating to inhibit task-irrelevant information along the same ascending afferent pathways (Staines et al., 2002). The primary somatosensory cortex has been associated with sensory gating (Knight et al., 1999) and the possible modulation of touch perception, by down-regulation of irrelevant sensory input, can aid patient groups with altered touch perception. This could be made possible through targeted application of cTBS and the modulation of underlying cortical excitability.

There are several limitations that require consideration in the present experiment since they impact the interpretation of the results. The first relates to the location of TDT measures. It

has been shown using the CM device that values of TDT are not different between the hand

dorsum and digit tips (Tommerdahl et al., 2007) but there is still a question of whether the

application of a plasticity inducing TBS paradigm might have yielded different results if

measures were taken from the digit tips. Further it is unclear if the effects are limited to the

contralateral hand or if bilateral changes could be induced by cTBS. Physiological effects of

cTBS over SI were examined bilaterally and only showed SEP suppression following right-

median nerve stimulation (Ishikawa et al., 2007). Previous examination of the effects of iTBS on

spatial acuity were limited to the contralateral hand (Ragert et al., 2008) however given this task

involves differing cortical processes it is possible that there could be a bilateral effect. Further, it

is unclear whether changes in tactile perception after the application of cTBS are limited to

temporal acuity or if the same direction and extent of effects could be seen through spatial

measures.

The examination of the effects following cTBS over the specific time course followed in

this study reveals trends that were not previously noted. The frequency of testing allowed

capturing of the effects at time points that in other studies were not examined (Ishikawa et al.,

2007; Katayama et al., 2010). This highlights the importance of testing frequency and the

lengthened duration of psychophysical effects compared to previous physiological studies. In

particular, the lack of effect at post 2 (7-10 minutes) was a novel finding that countered

hypothesized effects following cTBS application. It is possible that the choice of sampling TDT

values at such frequent intervals allowed for this novel finding reflecting first an immediate

short-lived impairment from 3-6 minutes followed by a slow building but sustained impairment

at 11-18 minutes. The aforementioned mechanisms could explain the differential onset and

latency of the effects. Further, by examining the dynamics of the changes in TDT over the

specific intervals tested provides a means to map out the time-course of effects of cTBS. The time blocks tested were atypical of those that have previously examined physiological and psychophysical measures following TBS. One comparable study by Huang et al. (2005) tested the effects of TBS over M1on the amplitude on MEPs for every minute for the first 6 minutes following TBS and then at an average of 2 minute intervals. The pattern of effects, while not directly translatable, follows a comparable pattern that was exhibited in this study. In that study, following iTBS application the facilitation of MEP amplitude was most evident from 1-5 and 15-19 minutes but not evident from about 7-13 minutes (Huang et al., 2005). These results were replicated in two other studies following the same testing paradigm (Huang et al., 2007; 2008). With Experiment 1 the effects were most evident from 3-6 and from 11-18 minutes but not from 7-10 minutes following TBS application. This exemplifies how the frequency of testing can aid in revealing patterns of effects that might not otherwise be noticed.

Overall, the present study demonstrated that cTBS over SI impairs temporal tactile perception on the hand. This is the first known report of the effects of TBS on temporal acuity on the hand. These findings are in line with previous findings and give insight into the possible mechanisms and applications of cTBS in modifying tactile acuity on the hand.

Chapter 4: Experiment 2
Modulation of tactile spatial discrimination on the hand following continuous theta-burst stimulation over the primary somatosensory cortex

4.1 Introduction

Tactile spatial acuity may be defined as the ability to localize two distinct stimuli on a skin surface through detecting and discriminating differences in the applied stimuli. Psychophysical investigations of tactile perception reveal the importance of spatial acuity to the integrity of underlying neural function as spatial acuity is altered on the hand in patient's suffering from neurological disorders such as Parkinson's disease (Sathian et al., 1997; Zia et al., 2003) and focal hand dystonia (Bara-Jimenez et al., 2000; Sanger et al., 2001). It is thought that tactile perceptual impairments may contribute to the severity of motor symptoms exhibited in these disorders. Identifying means to alter tactile spatial acuity may have implications for altering motor control. However, a precursor to altering spatial acuity in neurological populations is to identify reliable means of modulating such tactile perception in healthy individuals. Repetitive transcranial magnetic stimulation (rTMS) offers such an opportunity and when applied over cortical areas that process touch information such as the primary somatosensory cortex (SI) can change tactile perception (Knecht et al., 2003; Satow et al., 2003; Ragert et al., 2003; 2004; Tegenthoff et al., 2005; Karim et al., 2006; Pledger et al., 2006). To date, few studies have attempted to modulate activity within SI in an attempt to alter spatial acuity. However, if acuity can be modified through rTMS application on healthy individuals there is potential for testing in patient groups whereby altered touch perception is thought to contribute to impaired motor control of the hand.

Another form of rTMS, referred to as theta-burst stimulation (TBS) modulates the amplitude of somatosensory evoked potentials (SEPs) (Ishikawa et al., 2007; Ragert et al., 2008; Katayama et al., 2007; 2010; Premji et al., 2010) when applied over SI. Further, in addition to altering physiology within SI, TBS delivered in the intermittent form (iTBS) can also modify tactile spatial acuity (Ragert et al., 2008). In the latter study an improvement in spatial tactile perception using two-point discrimination was observed for up to 30 minutes following iTBS. The time course of these perceptual changes appear to parallel those seen in the SEP physiological studies (Ragert et al., 2008; Premji et al., 2010; Katayama et al., 2010). To date no other measures of tactile spatial acuity have been examined following iTBS application. In particular, the other form of TBS that involves pulses applied continuously (cTBS) to the targeted cortical area may induce changes in tactile spatial acuity but has yet to be determined. The cTBS paradigm when applied over SI (Mochizuki et al., 2007; Poreisz et al., 2008) and other non-motor areas (Franca et al., 2006; Koch et al., 2007) has been shown to consistently induce an inhibitory effect on the stimulated cortex while the effects of iTBS were more variable over the same non-motor areas.

Amplitude discrimination is a measure of tactile acuity whereby the intensity of the contact from two probes is compared across different skin sites (Tannan et al., 2007a). While the distance between the probes is maintained, the intensity of the vibrotactile stimuli is adjusted to make it easier or harder to discern the differences in stimulus amplitude and identify which probe delivered the more intense stimulus. This shift in intensity between the two skin sites modifies the comparison across the skin surface in that the amplitude changes alter the ability to discriminate points in space (Zhang et al., 2008). For this reason, amplitude discrimination has been considered to be within the domain of spatial acuity. Amplitude discrimination has been

used in many studies to examine spatial acuity in healthy individuals (Tannan et al., 2007a; 2007b; Folger et al., 2008; Francisco et al., 2008; Zhang et al., 2009) and autism (Tannan et al., 2008). Compared to other measures of spatial acuity such as two-point discrimination, amplitude discrimination bares particular advantages. First, static indentation of probes fails to recruit all afferent types associated with natural stimulation of the skin (Tommerdahl et al., 2010). It has been shown that vibrating tactile stimuli activates all receptor and afferent types and overcomes the above issue and can lead to better acuity compared to static indentation (Vierck and Jones, 1970; Tannan et al., 2005). Further, two-point discrimination has been criticized for its subjective and limiting criteria (Zhang et al., 2008; Craig and Johnson, 2000). The dependent measure of amplitude discrimination utilized in this study applies vibrotactile stimuli that are modified in their intensity on a trial-by-trial basis and provides a reliable means to assess tactile spatial acuity.

From the results of Experiment 1 it was determined that tactile temporal acuity could be modulated following cTBS application over SI. Temporal discrimination threshold (TDT) values were elevated immediately following and again from 11-18 minutes post stimulation. It is unknown whether cTBS over SI modifies spatial acuity, and in particular, the spatial measure of amplitude discrimination. The present study investigated the influence of cTBS over left SI on amplitude discrimination on the right hand. The cTBS paradigm was applied to examine if measures of spatial tactile perception could be modulated and over what time course would these effects persist. Following the same sampling frequency as Experiment 1, amplitude discrimination was measured before and following cTBS at 3-6, 7-10, 11-14, 15-18, 23-26, and 31-34 minutes. Sampling over this time course allows for the examination of TBS effects in detail and can aid understanding the extent and duration of changes in cortical excitability caused

by this plasticity inducing protocol. It was hypothesized that cTBS would increase the amplitude discrimination threshold such that tactile perception would be impaired for up to 18 minutes in line the perceptual changes in TDT (Experiment 1) and physiological measures (Ishikawa et al., 2007; Katayama et al., 2010).

4.2 Methods

4.2.1 Participants

Eight subjects (4 females, mean age 28 years ± standard deviation (SD) 4.3 years) participated. Right-handedness was determined using a subset of the Edinburgh Handedness Inventory (EHI) (Oldfield, 1971). All subjects were required to give informed written consent prior to study participation. The study was approved by the Office of Research Ethics at the University of Waterloo and conformed to the Declaration of Helsinki.

4.2.2 Experimental approach

The experimental paradigm used for Experiment 2 followed that for Experiment 1 (Chapter 3) with the following exceptions:

Psychophysical Task

Using the Cortical Metrics (CM) device (Tannan et al., 2007a) amplitude discrimination measures were collected immediately preceding cTBS and at six time blocks following: 3-6, 7-10, 11-14, 15-18, 23-26, and 31-34 minutes, using the same sampling frequency as Experiment 1. All psychophysical measures were conducted in a quiet room with the subject seated at a table with a laptop monitor positioned in the center, the CM device to the side, and a computer mouse for response selection on the opposite side as the CM device. Subjects placed their dorsum of

their right hand under the device opening to allow the plastic probes of the device to lower until a registered force of 0.1 g. The CM device then further indented the two probes by 500 microns to ensure skin contact prior to stimulation onset. The interprobe distance was set at 32 mm and remained constant throughout. All CM protocols were run through programs designed with LabView (v 8.5, National Instruments Corporation, Texas, USA).

Training Trials

At the start of the experiment three sets of training trials for the amplitude discrimination task were performed. Training trials were included to familiarize subjects with the task before commencing the testing trials. Training trials were performed in three blocks to ensure subjects had an ample number of trials to learn the task and so trends across these training trials could be later examined. Each block required participants to perform the amplitude discrimination task and obtain 5 correct consecutive responses. For the training trials the amplitude of stimulation of the two probes differed by 100 microns (200 vs 100). During the training trials, subjects indicated their readiness to begin by making a mouse click. During training trials visual feedback was given via the laptop monitor and indicated to participants whether their response was correct (happy face, 'good job!') or incorrect ('please try again').

Test Trials

Following the training trials, the location of the probes on the right hand dorsum was marked to aid in alignment of the probes to the same skin site for subsequent trials. The first block of test trials began immediately following the training. For each test block subjects indicated their readiness by making a mouse click. For each testing trial the two probes were vibrated simultaneously for 500 msec at a constant frequency of 25 Hz. One probe (the *standard*) was set at 100 micron indentation and the other probe (the *test*) was set at 200 microns

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at the start of the testing trials. Following delivery of the vibrotactile stimuli the subject was

queried to respond as to which probe site received the more intense stimulus. Subjects

responded by selecting the appropriate mouse click (left for left probe, right for the right probe).

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 microns on 1 up/1 down

response for the first 10 trials and 2 up/1 down for the last 10 (two correct responses decreased

the amplitude of indentation by 10 microns while one incorrect response increased the amplitude

of indentation by 10 microns). Therefore, a correct response resulted in the amplitude of the *test*

stimulus decreasing by 10 microns making the task harder to perform. The adjustment from the

1 up/1 down to a 2 up/1 down protocol was used as it has been previously shown this allows for

a reliable and accelerated means to obtain threshold values (Tannan et al., 2007a; 2007b; 2008;

Folger et al., 2008; Zhang et al., 2009). The amplitude of the *standard* probe remained constant

at 100 microns throughout all test trials. The site of the *standard* and *test* probe was randomly

selected on a trial-by-trial basis. Trials were separated by a minimum of 5 seconds and subjects

were prompted by visual cues displayed on the laptop monitor in advance of the next trial. Each

block consisted of 20 trials collected over 2.5 minutes. Auditory cues were minimized by the use

of earplugs during training and test trials. Further, all training and testing trials were video-

recorded for quality assurance purposes. A schematic of the amplitude discrimination task is
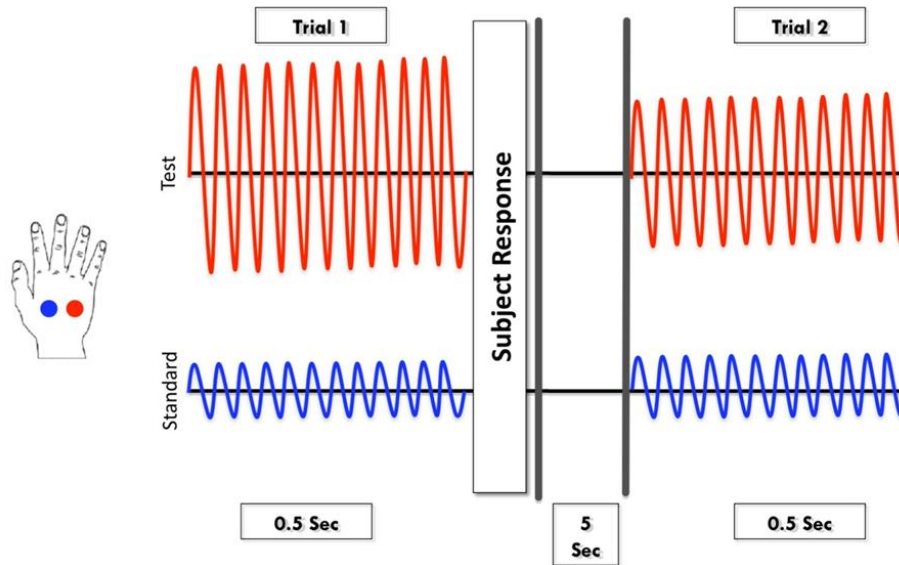
shown in Figure 4.1.

Figure 4.1: Amplitude Discrimination. Two trials are shown with correct subject response resulting in lowering of test amplitude. Figure adapted from Zhang et al., 2009

4.2.3 Data Analysis

The amplitude discrimination thresholds obtained from the last five trials (trials 16 to 20) were averaged to obtain each subjects threshold for the psychophysical task (Tannan et al., 2007a; 2007b; 2008; Folger et al., 2008; Zhang et al., 2009). Figure 4.2 displays an example of a testing trial for one participant.
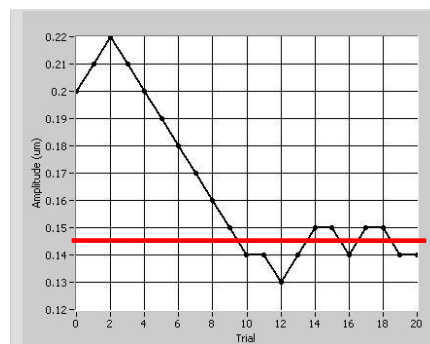

Figure 4.2: Amplitude discrimination. A sample of one subject's testing trials for this task is given. To establish subject's threshold the average of the last 5 trials (Tannan et al., 2007a; 2007b; Folger et al., 2008; Francisco et al., 2008; Zhang et al., 2009) is calculated, shown above as red dashed line.

For the training trials, the total number of trials performed by an individual to successfully complete each of the three training blocks was quantified. As described earlier, five correct and consecutive responses were required to end a block of training trials. The number of trials for each block was averaged for the group and plotted. To determine any improvements in performance across the blocks a Friedman test with Bonferroni corrected contrasts (corrected for three comparisons, block 1 versus block 2, block 1 versus block 3, and block 2 versus block 3) was conducted to compare performances between the first and subsequent training blocks. Statistical significance was set at $p \leq 0.05$.

One-way repeated measures analysis of variance (ANOVA) with within-subject factor 'TIME' (7 levels; pre, post 1, post 2, post 3, post 4, post 5, post 6) was performed for the testing trials. A priori hypotheses were tested using contrast estimations and Bonferroni correction (corrected for 4 comparisons, pre cTBS versus post 1, pre cTBS versus post 2, pre cTBS versus post 3, and pre cTBS versus post 4). To correct and test for sphericity, the Huynh-Feldt (H-F) estimate was used when necessary to reveal whether the data violated the assumptions of the ANOVA. Post-hoc analysis was performed using Dunnett's test to test for any other differences following cTBS application. All statistical analysis was performed using SAS 9.2 Windows software (SAS Institute Inc., Cary, North Carolina, US). Significance was set at $p \leq 0.05$.

4.3 Results

All participants successfully completed the experiment. The mean active motor threshold (AMT) for the tested participants was 49 ± 8.3 % of the stimulator output with cTBS being delivered at $39 \pm 6.6\%$.

4.3.1 Training trials

All subjects completed three blocks of training. The group-averaged means (with standard errors) for the training trial blocks are shown in Figure 4.3. The y-axis describes the total number of trials performed to reach the criteria of 5 correct consecutive responses. All subjects showed improvement in ability to perform the task and were able to complete the last training block in fewer trials than required for block 1 and block 2. By Block 3 a total of 9 ± 6.2 (SD) trials were required before reaching the performance criteria. These data suggest that subjects were able to understand the task instructions and were able to perform the task with improvement from across the blocks. Further, application of the Friedman test showed a significant main effect of BLOCK ($F_{(2, 7)} = 4.50$, $p = 0.0310$). Specific contrasts were run to examine pair-wise differences in performance between the first and second as well as the first and third training block. Bonferroni corrected contrasts revealed significantly lower amplitude discrimination training performance scores for the third block compared to the first block ($p = 0.0118$). There was no significant difference between the first and second training block scores or the second and third training block scores.

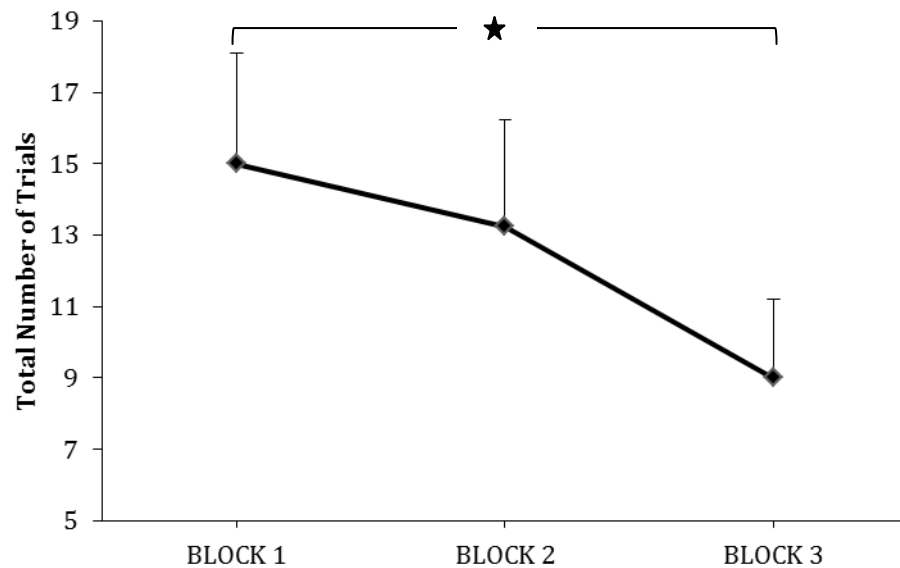## Training Trials: Amplitude Discrimination

Figure 4.3: Results from training trials for the amplitude discrimination task (N = 8). Subjects were required to complete three blocks of training with five correct responses required to complete a block. Total number of trials is reported. Asterisks above the time interval note statistical significance. Error bars represent standard error of the means.

4.3.2 Test trials

The pre cTBS amplitude discrimination threshold values for the eight subjects tested was 132.7 ± 21 microns (SD) which equates to a difference limen of 32.7 microns (132.7 *test* versus 100 micron *standard* amplitude). The ANOVA revealed a significant main effect of TIME ($F_{(6, 42)}$ = 4.17, p = 0.0023, H-F p = 0.0060). Figure 4.4 displays the group-averaged amplitude discrimination values (with standard error) at each time block tested. In support of the hypotheses, a priori contrasts revealed that measured thresholds significantly greater at post 1 (3-6 minutes, p = 0.0016), post 2 (7-10 minutes, p = 0.0116), post 3 (11-14 minutes, p = 0.0006) and post 4 (15-18 minutes, p = 0.0004) time blocks following cTBS. Table 4.1 displays the

number of participants who demonstrate the impairment in amplitude discrimination at the post 1, 2, 3, and 4 time blocks.

To examine the trends across all trials for the subjects tested additional analyses were conducted to determine if there were any differences in values from other trials in addition to the calculated last 5 (trials 16-20). Figure 4.5 shows a plot of the group-averaged amplitude discrimination (with SD) thresholds for each trial. This plot reveals near constant threshold values from the last 10 trials (trials 11-20) and noting the relatively stable values from trials 11-20 additional analyses were conducted using the average of trials 11 to 15. A one-way ANOVA revealed no significant main effect of TIME ($F_{(6, 42)} = 2.30$, p = 0.0524, H-F p = 0.089). Figure 4.6 shows displays the group-averaged amplitude discrimination (with standard error) at each time block tested. For trials 11-15, Bonferroni corrected (for four comparisons) a priori contrasts revealed that the amplitude discrimination threshold was only significantly greater at post 1 (3-6 minutes, p = 0.0086) compared pre cTBS values.

Amplitude Discrimination
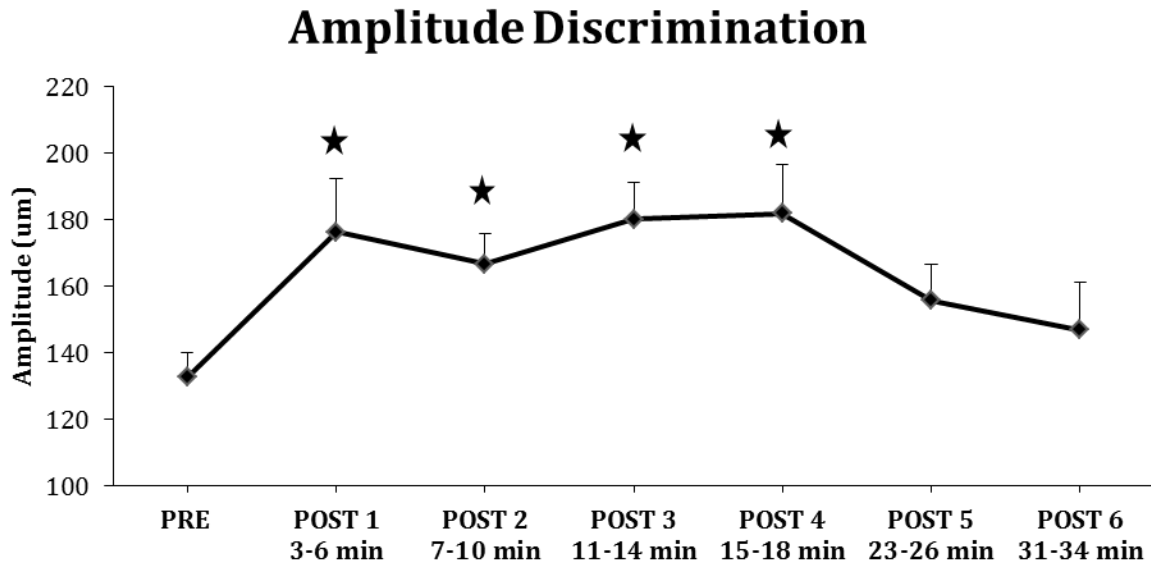
Figure 4.4: Results from the last five testing trials for the amplitude discrimination task (N = 8). Threshold values were elevated post 1 (p = 0.0016), post 2 (p = 0.0116), post 3 (p = 0.0006) and at post 4 (p = 0.0004). Asterisks above the time interval note statistical significance. Error bars represent standard error of the means.

Amplitude Discrimination (N = 8)

	Post 1	Post 2	Post 3	Post 4
Increase	7	8	7	7
Decrease	1	0	1	1
No Change	0	0	0	0

Table 4.1: Summary of trends noted at post 1, post 2, post 3, and post 4 for all subjects tested compared to pre cTBS threshold values for the amplitude discrimination task.
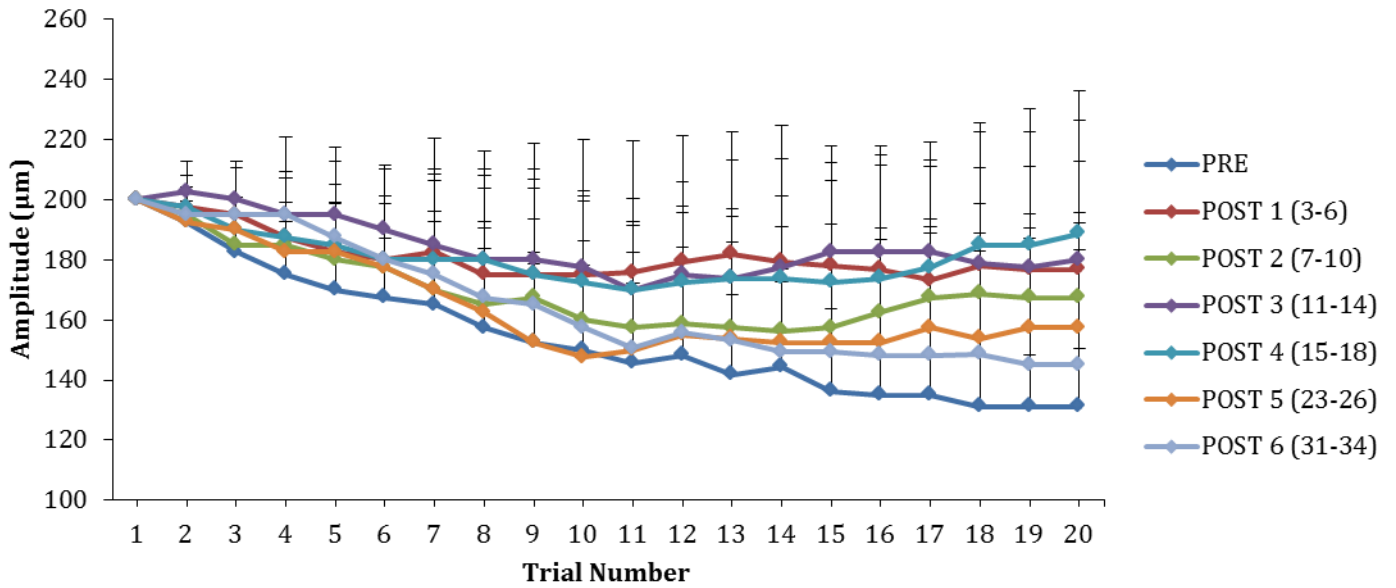
Figure 4.5: Results from all testing trials for the amplitude discrimination task (N = 8). Error bars represent standard deviation (SD).
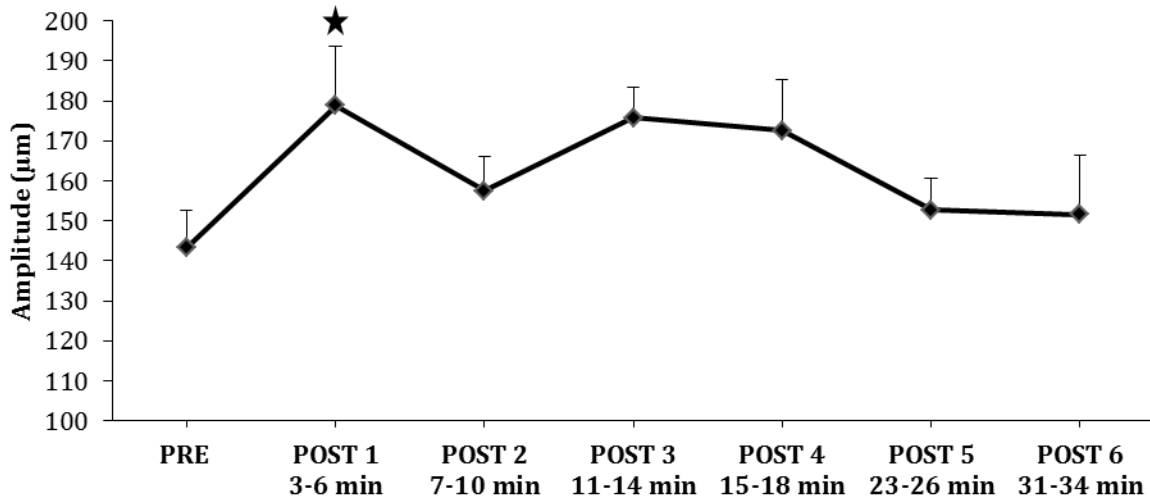

Figure 4.6: Results from testing trials 11-15 for the amplitude discrimination task at each time interval for all subjects (N = 8). Threshold values were elevated post 1 (p = 0.0086). Asterisks above the time interval note statistical significance. Error bars represent standard error of the means.

4.4 Discussion

The present experiment investigated the effect of cTBS over left SI on spatial tactile acuity on the dorsum of the right hand. This study reveals that amplitude discrimination is impaired such that thresholds are elevated following cTBS application at post 1 (3-6 minutes), post 2 (7-10 minutes), post 3 (11-14 minutes), and post 4 (15-18 minutes) time intervals. These perceptual data support the physiological results such that SEPs are depressed following cTBS over SI (Ishikawa et al., 2007). The duration of the perceptual after-effects from this experiment persist longer than physiological changes in SEPs amplitude (Ishikawa et al., 2007; Katayama et al., 2010). Potential mechanisms for the spatial measure of amplitude discrimination and the changes observed in this spatial perceptual threshold are discussed in the following paragraphs.

Amplitude discrimination is a measure of tactile spatial acuity that involves the delivery of vibrotactile stimuli to two adjacent skin sites. The adjusted intensity of indentation through subject response allows for a means to track how one perceives the tactile stimuli applied to multiple skin sites within and across trials (Tannan et al., 2007a). Importantly, the neural basis and coding of stimulus amplitude within SI has been extensively examined using optical imaging, neuroimaging, and neurophysiological studies (Simons et al., 2005; 2006; Chen et al., 2007; Muniak et al., 2007). These studies reveal that the cortical representation of vibrotactile stimulus intensity is proportional to the magnitude of the neuronal population response whereby an increase in stimulus intensity is associated with an increase in the firing frequency of individual neurons while the spatial extent of response remains relatively constant (Simons et al., 2005). In addition, increasing stimulus amplitude results in greater surround inhibition, also referred to as lateral inhibition, that encloses the perimeter of the activated cortical receptive field and creates contrast between signals within versus outside this site of activation allowing

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for better spatial resolution of the stimulus (Simons et al., 2005). It has been shown that amplitude discrimination as measured using the CM device follows Weber's law in that the ability to detect differences in intensity between two simultaneous stimuli changes in a linear fashion with increasing stimulus amplitude (Francisco et al., 2008). In this study, using the same paradigm as set in Experiment 2 with additional test conditions, it was examined how amplitude discrimination is tracked with altering initial *standard* site intensities with results revealing that changing the stimulus amplitude directly alters the ability to detect differences between the probes with an increased amplitude resulting in greater ability to detect differences (Francisco et al., 2008). Further, this linear association between vibrotactile stimulus delivery and its perception on the skin correlates with the magnitude changes in SI activity with increased amplitude (Francisco et al., 2008). In that manner, modification in the vibrotactile amplitude of the applied stimuli to the skin is reflected through changes in tactile discrimination that are related to changes in cortical activation within SI. Thus, amplitude discrimination is a measure of spatial acuity because of its ability to parallel changes in SI cortical activation within and between the activated receptive fields

Traditionally, the two-point discrimination method has been employed to track changes in spatial acuity in healthy and patient populations but this measure is criticized for not mimicking natural tactile stimulation (Tommerdahl et al., 2010) and its subjective nature (Craig and Johnson, 2000). One study has linked changes in stimulus intensity and two-point discrimination capabilities. This study conducted by Zhang et al. (2008) measured amplitude discrimination thresholds with varying interprobe distances. In that study it was revealed that through the modification of interprobe distances, particularly by reducing the distance between probes as per a two-point discrimination task, the ability to discern differences between the set

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amplitudes of two probes became impaired (Zhang et al., 2008). The amplitude of the probes was different throughout each experimental condition but held constant throughout all manipulations of the spatial positioning of the probes on the skin and the impairment of amplitude discrimination was observed through direct modification of the spatial localization of the stimulus on the hand. Importantly, the movement of the probes on the skin reflects changes in activation of separate receptive fields within SI and as the probes are moved closer it becomes harder to detect differences in amplitude due to lateral inhibition and possible overlap of cortical regions of activation (Mountcastle, 2005). With amplitude discrimination, the modulation of the intensity directly alters the surround inhibition and while the probes do not change their spatial location on the skin, the adjustment in amplitude modifies the cortical regions of activation by directly influencing neuronal firing and the lateral inhibition between the activated cortical fields (Simons et al., 2005). Specifically, by decreasing the amplitude of vibrotactile stimulation the neuronal firing within the activated cortical field is reduced as well as the extent of lateral inhibition and vice versa. This directly relates to the results seen by Zhang et al. (2008) in that the measure of amplitude discrimination follows the same pattern of threshold impairment due to the effects on lateral inhibition and ability to detect and discriminate between stimuli amongst two cortical receptive fields. By tracking how a subject is able to discern differences between the two vibrotactile stimuli that vary in intensity, the measure of amplitude discrimination actually captures how the neural representation of the stimuli is being spatially represented in SI and how actions of excitatory and inhibitory interneurons are being modified.

Amplitude discrimination thresholds before cTBS were comparable to those reported from previous studies using the cortical metrics device (Tannan et al., 2007a; 2007b; 2008; Folger et al., 2008; Francisco et al., 2008; Zhang et al., 2009) with the results from this study

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giving a difference limen of 32.7 ± 21 microns (between the *test* and *standard* stimulus).

Following cTBS application, the amplitude discrimination thresholds were increased for 3-18

minutes. Threshold values in microns with percent change from pre cTBS values were 176.4

(33% increase), 166.8 (26% increase), 180.3 (36% increase), and 182.0 (37% increase) for post

1, 2, 3, and 4 time blocks, respectively. The impairment in the threshold values noted from post

1 to post 4 time blocks or 3-18 minutes could be related to the role of cTBS on the local

interneurons within SI. Given the results of this study are in line with the direction of effects

exhibited in physiological SEP studies (Ishikawa et al., 2007; Katayama et al., 2010) it is

possible that similar mechanisms are mediating the suppression in cortical activity. In those

studies the effect of cTBS was attributed to the suppression of excitability within superficial

layers of SI (Ishikawa et al., 2007) with action on the GABAergic inhibitory interneurons

(Katayama et al., 2010). More specific to the results of Experiment 2, the effects of cTBS could

be attributed to the action of the inhibitory GABAergic interneurons that are thought to be

involved in modulation and regulation of cortical processing within cortical columns (Casanova

et al., 2006). Studies have shown that cTBS acts on inhibitory interneurons that control the input

to pyramidal neurons and can modify the action of particular proteins that are involved in

producing dendritic inhibition (Benali et al., 2011). Further, cortical imaging studies have shown

that cTBS activates GABA interneurons within the cortex (Stagg et al., 2009) with this

preventing further GABA neurotransmitter release. This loss of inhibition could explain the

increased amplitude discrimination threshold values as the spatial extent of lateral inhibition

between cortical columns could be directly modified by cTBS application. The ability to change

cortical excitability through the action of cTBS could provide means to alter tactile processing in

patient groups.

Why is the finding of suppressed tactile acuity important? It is possible that through the down-regulation of cortical processing as exhibited through impaired tactile perception that the same methodology could be used to target specific cortex that can aid in regulating relevant cortical processing within SI. This has clinical applications for patient populations that could have issues with sensory gating or the inability to modulate task-relevant and inhibit task-irrelevant stimuli. Such is the case in patients with autism spectrum disorder (ASD) and cerebral palsy (CP) (Cascio et al., 2008). It is known that the hypersensitivity to tactile stimuli can result in abnormal responses to otherwise innocuous touch (Cascio, 2010). In the case of CP somatosensory processing impairments have been linked to motor deficits (Van Heest et al., 1993) with specific attention to the hyper-responsiveness of CP patients to tactile stimuli.

Similar to the limitations of Experiment 1 and the TDT measure there are several limitations to this study including the location psychophysical measures on the hand dorsum and if the effects are limited to the contralateral hand or if bilateral changes could be induced by cTBS. Previous studies examining changes in tactile spatial discrimination following iTBS showed the effects were limited to the contralateral side (Ragert et al., 2008) but it is possible that the effects of cTBS could differ. Further, Experiment 2 examined changes in tactile perception when only the one percept, of amplitude discrimination, was being applied through the two probes. It is possible that with the addition of a distracter irrelevant stimulus applied to the hand at the same time the subject is asked to perform the amplitude discrimination task the results would be modified and could better examine if changes in this spatial measure are applicable to clinical populations.

Overall, the present study demonstrated that cTBS over SI impairs spatial tactile perception on the hand. This is the first report of the effects of cTBS on tactile spatial

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discrimination to our knowledge. These findings are in line with the direction of previous physiological (Ishikawa et al., 2007; Katayama et al., 2010) and psychophysical studies (Experiment 1) that have examined the effects of cTBS over SI. Experiment 2 provides further insight into the possible mechanisms and applications of cTBS in modifying tactile acuity on the hand.

Chapter 5: General Discussion

The Master's thesis examined the effect of continuous theta-burst stimulation (cTBS) applied over the primary somatosensory cortex (SI) on tactile perception on the hand. Two studies were conducted to investigate whether temporal and spatial tactile discrimination on the dorsum of the right hand may be modulated following cTBS over left SI. Both experiments examined changes in tactile perception before and following cTBS at six time blocks: 3-6, 7-10, 11-13, 15-18, 23-26, and 31-34 minutes. Results from both experiments showed that cTBS over SI impairs temporal and spatial tactile perception on the hand. This impairment, reflected in elevated tactile discrimination thresholds, persisted for up to 18 minutes following cTBS. These data provide insight into the neural mechanisms involved in cTBS and how tactile percepts could be modified to aid patient groups with altered sensory function on the hand. The following discussion will outline the importance of these findings and the possible neural mechanisms that explain how touch perception could be modified through the application of a plasticity inducing protocol such as cTBS.

Time course of changes in spatial and temporal percepts

The results of Experiments 1 and 2 revealed that the application of cTBS suppressed tactile perception on the hand for up to 18 minutes. Both measures of tactile discrimination thresholds, temporal and spatial, were modulated similarly in time. Figure 5.1 visually compares the specific time course of threshold impairments for the spatial and temporal tactile tasks. Displayed is the group-averaged data from the last five trials for all participants in each task before and at all time points measured following cTBS. It is interesting to note the 'worsening' of tactile acuity that occurs for both tasks at the same time blocks; post block 1 (3-6 minutes) and

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4 (15-18 minutes). Statistically, the greatest impairment for each task was slightly different but the overall temporal pattern of changes suggests strong similarities. For both tasks, threshold values at post block 2 (7-10 minutes) show impairments that are less than those in the preceding and following time blocks. Further, both tasks reveal a return to pre cTBS values from post blocks 5 and 6. The opportunity to reveal the similarities between the tactile tasks is a product of the high sampling frequency used in the present studies. Without sampling approximately every four minutes, the closeness of the time course of effects may have been missed. The findings of the thesis studies have important implications for identifying the effects of TMS protocols and suggest that if characterizing the time course of effects is important, then a good approach is to sample the effects of TMS protocols frequently.

The relationship between tactile perception and physiological measures in SI

Tactile psychophysics and physiological measurements such as somatosensory evoked potentials (SEPs) can be used as indicators of the integrity of neural processing within SI. Alterations to either measure indicate changes in the ongoing neural function within SI. To understand how touch perception is modified we can use the information obtained from SEP studies. Specifically, an increase in SEP amplitude is associated with an increase in tactile acuity (Werhahn et al., 2002; Hoffken et al., 2007; Ragert et al., 2008). Conversely, a decrease in SEP amplitude is associated with impaired tactile acuity (Staines et al., 2002; Tamura et al., 2008). One measure of SEPs involves high-frequency oscillations (HFO) that are also associated with underlying somatosensory cortical activity. In a similar manner, decreased HFO amplitude has been associated with suppressed SEP amplitudes in patient groups with altered tactile perception (Cimatti et al., 2007). With the knowledge that tactile perception and amplitudes of

physiological measures such as SEPs/HFOs are reflecting common changes in underlying neural activity, we can begin to understand how TBS protocols affect tactile perception.

Mechanisms of cTBS on SI physiology and perception

The neural mechanisms of cTBS are not clear however inspection of the SEP and HFO data allow some insight. Previous work examining the effects of cTBS over SI demonstrates a decrease in the amplitude of both SEPs and HFOs (Ishikawa et al., 2007; Katayama et al., 2010). The effect of cTBS on SEPs was revealed only at two time intervals following stimulation (0-3, 10-13 minutes) and did not persist at 20 minutes following stimulation (Ishikawa et al., 2007). The cortical origins of SEPs are considered to result from the excitatory postsynaptic potentials of the apical dendrites of pyramidal neurons (Allison et al., 1991). The action of cTBS on the superficial layers of SI could suppress the cortical excitability of the pyramidal neurons that is reflected in the SEP amplitude suppression (Ishikawa et al., 2007). Further, the amplitude of HFOs was depressed at 15 minutes following cTBS over SI (Katayama et al., 2010). The late subcomponent of HFOs is thought to reflect actions of GABAergic inhibitory interneurons within layer 4 of SI (Hasimoto et al., 1996). It is possible that the action of cTBS at the later onset (i.e. 15 minutes) could act on the inhibitory interneurons underlying the targeted SI cortex and results in a suppression of HFO amplitude (Katayama et al., 2010). Combined, the effects of cTBS on the physiological measures of SEPs and HFOs reveal possible means with which TBS is able to modulate cortical processing within SI.

To speculate what the neural mechanisms of cTBS on tactile perception may be, it is important to consider the underlying mechanisms of spatial and temporal perception. Temporal acuity is mediated via in-field inhibition whereby inhibition within the activated cortical

receptive field results in a subsequent decrease in neuronal firing (Gardner and Costanzo, 1980; Laskin and Spencer, 1979). Measures of spatial acuity occurs with the application of simultaneous stimuli within adjacent receptive fields that results in a decrease in the area and amplitude of cortical neuronal activation between receptive fields due to lateral inhibition between activated receptive fields (Friedman et al., 2008; Chen et al., 2003). CTBS, which may modify SEPs via changes in the excitability of pyramidal neurons, may affect spatial and temporal perception similarly. When cTBS is applied over SI, the extent of lateral inhibition is modified via the initial suppression of excitability of pyramidal neurons (Ishikawa et al., 2007) responding to the tactile input. This pyramidal neuron population will then be no longer as strongly excitable to applied tactile stimuli and will therefore create a reduction in the surround inhibition. This reduced lateral inhibition can in turn result in decreased spatial acuity. Further, the decreased excitability within the focus of the activated pyramidal neurons following cTBS will result in in-field inhibition due to the suppression of neuronal activity that can impair temporal acuity. In that manner, if cTBS acts on SI pyramidal neurons it can alter both the activation of the cortical receptive field and neighboring ensembles resulting in impaired tactile acuity.

An alternate explanation for the effects of cTBS on tactile perception may relate to GABAergic inhibitory interneurons. Studies have shown that cTBS acts on inhibitory interneurons that control the input to pyramidal neurons and can modify the action of particular proteins that are involved in producing dendritic inhibition (Benali et al., 2011). Further, cortical imaging studies have shown that cTBS activates GABA interneurons within the cortex (Stagg et al., 2009) with this preventing further GABA neurotransmitter release. Specific to the results of Experiment 1 and 2 the role of GABA and modulation of its uptake/expression may relate to

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tactile acuity. GABA mediated inhibition is directly related to receptive field size (Hicks and Dykes, 1983) and administration of a GABA antagonist that would hinder lateral inhibition results in increased receptive field size (Alloway and Burton, 1990; Chowdhury and Rasmusson, 2002). Tactile acuity is inversely related to the receptive field size of SI neurons and increased receptive fields reflect lower tactile acuity (Serino and Haggard, 2010). In that manner, if cTBS acts on GABAergic inhibitory interneurons by decreasing their responsiveness and activation, tactile perception would be impaired by directly impacting the spatial contrast between activated receptive fields due to a reduction in the lateral inhibition. This explanation could account for the spatial but not necessarily the temporal impairments although any modification in receptive field size and activation would impair both aspects of touch.

Other factors that modulate tactile discrimination

Processing tactile stimuli within SI can be influenced by factors besides the stimulus parameters. Studies have revealed that there is an attentional component to cortical activation within SI (Johansen-Berg et al., 2000) and the role of attention can be altered through task-relevant modulation (Nelson et al., 2004; Dionne et al., 2010). Further, it is also necessary to consider that lengthened experimental protocols can hinder attentional drive due to fatigue. Independent of task specifics, peripheral level factors can also influence tactile discrimination as stimulus detection can be altered depending on the density of mechanoreceptor innervation at the skin site of stimulation (Mountcastle, 2005) as well as any neuropathies that can alter the transmission and integration of afferent information (Rothwell et al., 1982). While the participants tested in both Experiments conducted for this thesis were healthy humans with no known neurological or peripheral disorders it is still important to consider these factors when examining perceptual thresholds obtained on patient groups or using differing methodology.

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Cortical and subcortical areas that contribute to tactile discrimination

There are several cortical and subcortical structures in addition to SI that are involved in tactile perception and performance on spatial and temporal tasks. Neuroimaging studies have revealed several cortical areas that are activated during temporal and spatial discrimination tasks including the secondary somatosensory cortex, prefrontal cortex, inferior parietal lobule, basal ganglia, cerebellum, premotor cortex and the supplementary motor area (De Lafuente and Romo, 2006; Rao et al., 2001; Pastor et al., 2004; Lacruz et al., 1991). The parallel and serial activation of other cortical areas adjacent and distant from SI could account for the noted elevation in both TDT and amplitude discrimination thresholds following cTBS. While the region of interest of this thesis work was SI, the application of CTBS can act to alter neural activity within remote loci that are anatomically connected with the targeted cortex (Ishikawa et al., 2007). The results from the Master thesis experiments reveal that it is possible that other cortical areas could have contributed to tactile discrimination such that temporal and spatial thresholds were elevated but not abolished following cTBS and were not as diminished as the impairments seen in patient groups that have abnormalities in loci beyond SI.

Importance of tactile discrimination

Hand movements may emphasize temporal or spatial aspects of touch or their combination. With respect to the temporal features of touch, several studies have examined how loss of tactile perception can impair the timing of successive movements. Studies by Johansson and Westling (1984; 1987) show the importance of tactile information for transitions from a grasp to lift phase in a precision grip task. It was revealed that loss of tactile afferent information resulted in a prolonged transition between these movement stages. Specific to the spatial

features of touch, removing tactile afferent information can result in inaccurate movements and lack of error detection. In particular, by anesthetizing the digit tips of skilled typists (Gordon and Soechting, 1995) or by simply having them elevate their hands above the keys (Terzuolo and Viviani, 1980) a decrease in spatial accuracy was observed such that digits were placed on incorrect keys. These data support the suggestion that tactile spatial acuity is important in movement accuracy and error detection. The combination of temporal and spatial features of touch are apparent in fine manipulation that involve tool use such as a writing utensil (Rothwell et al., 1982), tactual identification of objects (Motomura et al., 1990), and exploration of the environment (Jones and Lederman, 2006). Modifying spatial, temporal or both aspects of touch perception may result in changes to the movements of the hand that rely on those inputs.

Why the modulation of tactile perception is important

The down-regulation of tactile perception could aid clinical groups such as patients suffering from autism or cerebral palsy as these clinical groups have been associated with hyper-responsiveness and even tactile defensiveness, a term used to describe a hyperactive response to innocuous stimuli (Cascio, 2010). It is thought that sensory gating mechanisms, those that inhibit processing of task-irrelevant with facilitation of task-relevant information, play a role in regulating cortical processing within SI (Staines et al., 2002). SI is associated with this sensory gating (Knight et al., 1999) and possible modulation of tactile perception could alter sensory processing and aid in sensory gating of task-irrelevant stimuli. Other clinical groups such as patients with focal hand dystonia, Parkinson's disease, and stroke may demonstrate concomitant impairments in tactile perception and movement (Abbruzzese and Berardelli, 2003; Machado et al., 2010; Carey, 1995). There is emerging evidence that improving tactile perception may

improve the motor symptoms within these patient groups (Zeuner et al., 2002; 2003; Yekutiel and Guttman, 1993; Carey et al., 1993; 2005; Smania et al., 2003; Schneider et al., 2010).

Future avenues and significance

This thesis has shown cTBS over left SI can modulate tactile temporal and spatial perception on the right hand dorsum. Future studies can use this fundamental work to expand this focus to include other hand surfaces such as the fingers which exhibit greater between-subject variability due to their use-dependent cortical representations (Serino and Haggard, 2010). This will be important because the effects of cTBS may be differentially expressed within and between these skin sites. Other future avenues of this work could test whether the effects of cTBS on tactile discrimination of the ipsilateral hand. Determining if there are any bilateral influences is important as normal hand functioning and somatosensory integration incorporates inputs from both hands. Further, this thesis has focused on cTBS and demonstrated impairments. It would be very beneficial to find methods to improve tactile perception and it is possible that other forms of TBS such as intermittent application would alter perception in this direction. Another interesting approach could examine the effect of cTBS on adaptation by applying a short-lasting stimulus to the probe sites before the actual vibrotactile stimuli the subject is asked to attend to. This would further reveal the neural constraints of both TBS and the extent of its actions over SI processing as the neural mechanisms associated with adaptation could give insight into the exact role of cTBS on SI cortical neurons. While the ability to extract neuronal processes from psychophysical measures is based on how the percept is encoded, additional information could be acquired from conducting physiological studies examining changes in SEPs and HFOs over the same time course as those examined in Experiment 1 and 2. Overall, this Master's thesis work provided novel neuroscience information regarding how tactile

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perception on the hand could be modified through the application of a plasticity inducing

protocol. The ability to change touch perception on the hand could have clinical importance to

patients who have altered somatosensory processing and can ultimately lead to improved motor
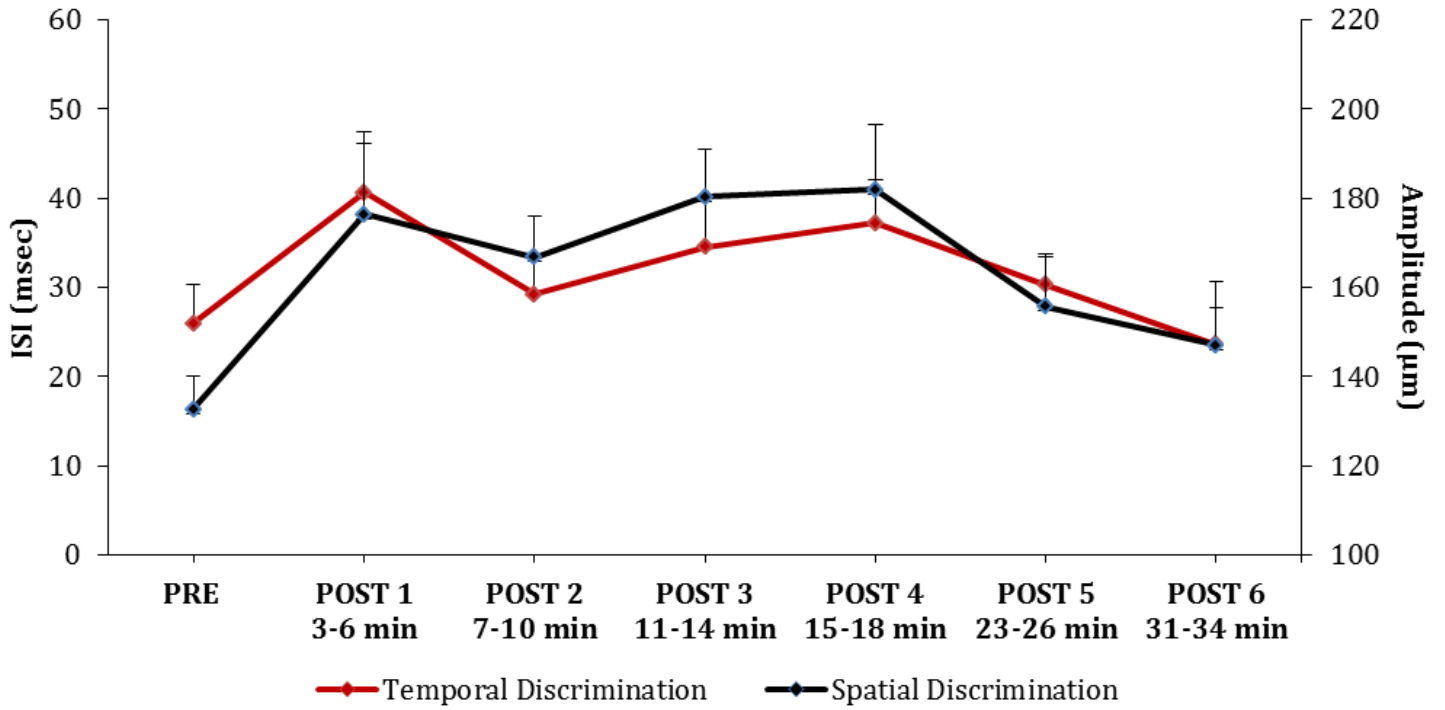
control of the hand.

Figure 5.1: Comparison of temporal and spatial thresholds results from Experiment 1 (Chapter 3) and 2 (Chapter 4), respectively. Error bars represent standard error of the means.

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