THETA BURST STIMULATION-INDUCED METAPLASTICITY: CHANGING TACTILE PERCEPTION AND PHYSIOLOGY IN PRIMARY SOMATOSENSORY CORTEX

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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

Theta-burst stimulation (TBS) over human primary motor cortex evokes plasticity and metaplasticity, the latter contributing to the homeostatic balance of excitation and inhibition. Our knowledge of TBS-induced effects on neighboring primary somatosensory cortex (SI) is limited and it is unknown whether TBS is capable of inducing metaplasticity within human SI. Sixteen right-handed participants (6 females, mean age 23) received six different TBS protocols delivered over SI in separate sessions. TBS protocols were delivered at 30 Hz (612 pulses) and included continuous TBS (cTBS), intermittent TBS (iTBS), cTBS followed by cTBS, iTBS followed by iTBS, cTBS followed by iTBS and iTBS followed by cTBS. Dependent measures included the amplitude of the first and second somatosensory evoked potential (SEP) following median nerve stimulation and their paired-pulse ratio (PPR), and temporal order judgment (TOJ) performed on digits 2 and 3. Dependent measures were obtained before and at 5, 25, 50 and 90 minutes following stimulation. Results indicate similar effects following cTBS and iTBS; increased amplitude of the second SEP with marginal changes to PPR, and elevated TOJ thresholds. CTBS-cTBS and iTBS-iTBS both demonstrated metaplasticity via measures of TOJ but with disparities in their direction and timing of effects. I conclude that 30 Hz cTBS and iTBS protocols delivered in isolation induce similar plasticity in SI as measured by decreases in SI intracortical inhibition and impairments in TOJ performance, and when applied in multiples, produce metaplasticity effects on TOJ performance.

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DESCRIPTIVE NOTE

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LIST OF ABBREVIATIONS

AMT	Active Motor Threshold
ANOVA	Analysis of Variance
AP	Anterior-to-Posterior
APB	Abductor Pollicis Brevis
Ca^{2+}	Calcium
CB	Calbindin D-28k
cTBS	Continuous Theta-Burst Stimulation
EEG	Electroencephalography
EPSP	Excitatory Post Synaptic Potential
FDI	First Dorsal Interosseous
GABA	γ-Aminobutyric Acid
GAD	Glutamic Acid Decarboxylase
GAT-1	GABA-Transporter 1
iHFS	Intermittent High-Frequency Tactile Stimulation
ISI	Inter-Stimulus Interval
iTBS	Intermittent Theta-Burst Stimulation
LTD	Long-Term Depression
LTP	Long-Term Potentiation
M1	Primary Motor Cortex
MEP	Motor Evoked Potential
MSO	Maximum Stimulator Output
N20	Negative 20
P25	Postitive 25
PA	Posterior-to-Anterior
PAS	Paired Associative Stimulation
pHFS	Peripheral High-Frequency Stimulation
PPI	Paired Pulse Inhibition
PPR	Paired Pulse Ratio
PV	Parvalbumin
RMT	Resting Motor Threshold
rTMS	Repetitive Transcranial Magnetic Stimulation
SEP	Somatosensory Evoked Potentials
SI	Primary Somatosensory Cortex
TBS	Theta-Burst Stimulation
tDCS	Transcranial Direct Current Stimulation
TDT	Temporal Discrimination Threshold
TMS	Transcranial Magnetic Stimulation
TOJ	Temporal Order Judgment

Chapter 1: Goals of Thesis

1.1 Overview of Thesis

The goal of the Master's thesis is to investigate the effects of metaplasticity within the human somatosensory cortex (SI) on physiology and tactile perception. Metaplasticity is the process by which the immediate state of plasticity within a cell influences the degree and direction of future plasticity within the same cell. Repetitive transcranial magnetic stimulation (rTMS) is one method that can be used to artificially induce plastic changes within SI which have been shown to exist for a period as long as 30 minutes after the protocol[1–4]. The effects of pairing multiple rTMS protocols to induce metaplasticity within SI remains largely unexplored. Metaplasticity is an important mechanism within the brain because it creates a homeostatic balance whereby levels of excitation and inhibition are regulated based on the previous state of the synapse. Neurophysiology studies focused in primary motor cortex (M1) provide support for the presence of metaplasticity demonstrating that pairing combinations of rTMS and peripheral electrical stimulation gives rise to a period of either heightened or suppressed excitability lasting longer than that typically seen with a single, unpaired protocol (for a review see[5]). This thesis investigates metaplasticity by evaluating whether delivery of a double TBS protocol produces different effects than than the delivery of a single protocol.

The research in this thesis probed three questions.

1. Do cTBS and iTBS evoke opposite effects when delivered to SI?
2. Do cTBS and iTBS demonstrate metaplasticity when they are delivered as single versus double protocols?

3. Can metaplasticity effects persist beyond those observed with single plasticity-inducing TBS protocols?

This thesis aims to contribute to our current knowledge of rTMS-induced plasticity by being the first study to investigate TBS-induced effects on SI in terms of physiology and tactile perception. By advancing metaplasticity research in SI this thesis will provide new insight into effective protocols to create lasting metaplastic changes within SI.

1.2 Experiment Summary

The Master's thesis is comprised of one primary experiment that investigates the opportunity to induce long-term potentiation (LTP) and long-term depression (LTD)-like effects in SI and their metaplasticity effects using the rTMS protocol called theta-burst stimulation (TBS). Sixteen healthy participants each received six TBS protocols designed to induce plasticity or metaplasticity in SI. The protocols were as followed: (1) unprimed intermittent theta-burst stimulation (iTBS); (2) unprimed continuous theta-burst stimulation (cTBS) alone; (3) cTBS followed by cTBS; (4) iTBS followed by iTBS; (5) cTBS followed by iTBS; and (6) iTBS followed by cTBS. All protocols took place a minimum of one week apart in order to avoid carry-over plastic effects from the previous session. Pre and post-intervention dependent measures included somatosensory evoked potentials (SEP), SEP paired pulse ratio (PPR) and tactile acuity measured using a temporal order judgment (TOJ) task. Results indicate similar effects following cTBS and iTBS; increased amplitude of the second SEP with marginal changes to PPR, and elevated TOJ thresholds. CTBS-cTBS and iTBS-iTBS both demonstrated metaplasticity via measures of TOJ but with disparities in their direction and timing of effects. In conclusion, 30 Hz cTBS and iTBS protocols delivered in isolation induce similar plasticity in SI as measured by decreases in SI intracortical inhibition and impairments in TOJ performance, and when applied in multiples, produce metaplasticity effects on TOJ performance.

1.3 Significance of Work

Plasticity has been a key topic of research, owing to its importance in allowing lasting changes to occur within many areas of the human brain. Primary somatosensory cortex has been demonstrated to have a propensity for plasticity both in animal models[6] and in humans[1–3,7–10] following the application of TMS. TBS has been cited as a rapid protocol, capable of producing both LTP-like and LTD-like changes within SI depending on characteristics including the frequency and intensity of delivery and the continuous versus intermittent protocol design[1,7]. Recently, TBS has been used to temporarily alter SI physiology as well as tactile perception with a time course of effects lasting up to one hour[11,12]. Ultimately, the goal of investigating the receptiveness of SI to TBS-induced plastic changes is to create a method for changing motor output which rather than operating within M1, instead acts via SI. Homeostatic metaplasticity is the process by which past plasticity can regulate future plasticity within a cell. The time course of TBS-induced metaplastic effects are typically longer lived than that seen in plasticity alone however these effects have to date been studied exclusively in M1[13]. The ability to replicate these effects in SI may heighten our capacity to perceive our tactile surroundings and may provide a future avenue for therapeutic protocols. This work has implications for a wide range of clinical populations including, but not limited to stroke, dystonia, spinal cord injury and Parkinson's disease to potentially improve recovery time as well as quality of life.

Chapter 2: Literature Review

2.1 The Somatosensory Cortex

2.1.1 Somatosensory Cortex Anatomy

The Somatosensory Cortex makes up the region posterior to the motor cortex and central sulcus in humans. SI has a somatotopic representation, continuous from the spinal cord[14] and is divided into four regions known as Brodmann areas 3b, 3a, 2 and 1. Collectively these areas are important in receiving and organizing afferent information. Each area receives sensory inputs from the thalamus and surrounding Brodmann areas. Area 3b is important for receiving cutaneous information and relaying this to each of the other areas [15–18]. This area also receives the densest concentration of projections from the glabrous pads of the fingers[19]. Area 3a is involved primarily in processing afferent information received from muscle spindles,[20–22] while areas 1 and 2 are respectively involved in processing tactile discrimination and shape recognition[14,23]. Extensive studies in non-human primates have greatly advanced the knowledge of receptive fields in SI. Area 3b contains a significant number of cells that respond to cutaneous stimulation and indentation[24–28] as well as having the greatest surface area of the 4 areas contributing to the representation of the fingers[29]. Damage or removal of 3b causes widespread functional deficits[30–32]. Disruption of the other Brodmann areas in SI (specifically areas 1 and 2) produce more localized effects resulting in a decreased ability to recognize textures or three-dimensional objects[23].

2.1.2 Somatosensory Evoked Potentials (SEP)

Somatosensory evoked potential is a measure of activity within the somatosensory cortex probed using sensory stimuli. In order to obtain SEPs, electroencephalography (EEG) electrodes with conductive paste are placed over specific locations on the scalp corresponding to the positions of SI and a non-SI reference area. These locations are determined using the international 10-20 measurement system[33]. The 10-20 system measures laterally from the central midline (Cz) by 20% of the total ear to ear distance, to determine the approximate location of M1 (C3) and 2 cm posterior from this point to locate SI (C3'). An additional electrode is placed at a reference site. Two components of the SEP are of particular interest, the negative 20 (N20) and positive 25 (P25) inflections of the SEP waveform (Figure 2.1). The N20 is characterized by a negative inflection approximately 20 ms following the median nerve electrical stimulus[34]. The N20 represents the latency at which pyramidal cells in area 3b of SI become excited and excite surrounding cortical pyramidal cells[35,36]. The P25 follows closely after the N20 and results from the depolarization of pyramidal cell dendrites in area 1[37].

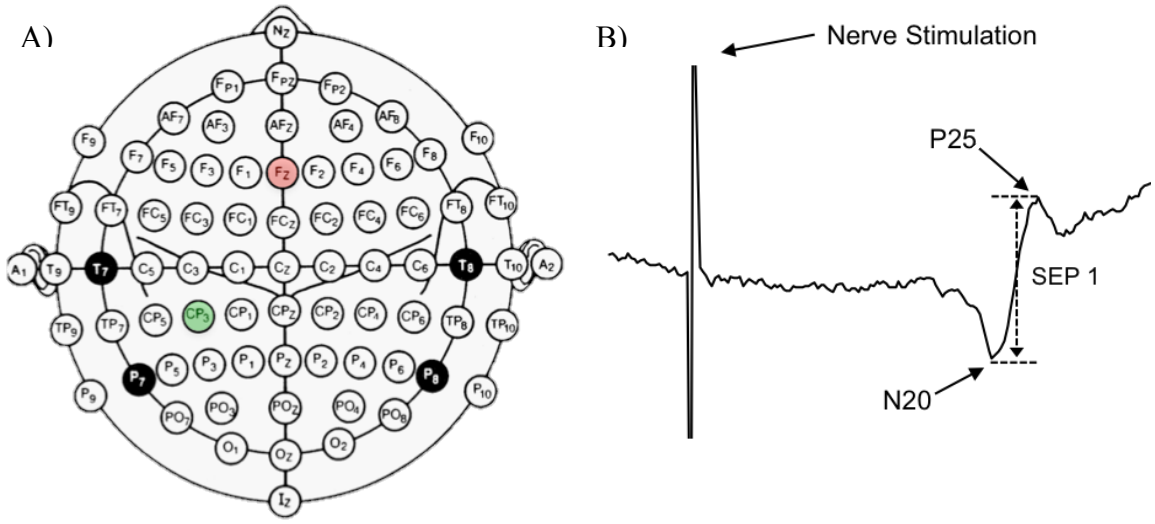

Figure 2.1 (A) International 10-20 system depicting placement of active (C3') and reference (Fz) electrodes. Modified from American Clinical Neurophysiology Society[38]. (B). Sample somatosensory evoked potential averaged trace.

The above latencies can be altered, particularly due to age and gender. Latencies are typically greater in males who tend to have longer limbs and thus afferent sensory information travels further to reach SI, however even when matched for height, these differences persist[34]. Age effects are greatest before adolescence with the most drastic increases in latencies occurring before age 17[34]. Stimulus intensity affects the SEP waveform, such that at higher stimulus intensities the N20-P25 amplitude is increased. Some studies have shown this relationship to be linear[39,40] while others show a plateauing of the effect[41] that appears to be visible at a wider range of stimulus intensities.

2.1.3 Somatosensory evoked potential paired pulse ratio (PPR)

Paired pulse inhibition occurs when two peripheral stimuli are delivered within a short window of time and the N20-P25 component of the SEP following the second pulse is substantially inhibited (2.2). This inhibition can be measured by calculating the paired

pulse ratio (PPR) between the SEP 1 and SEP 2. Typically an electrical stimuli is delivered to the median nerve to evoke a median nerve somatosensory evoked potential.

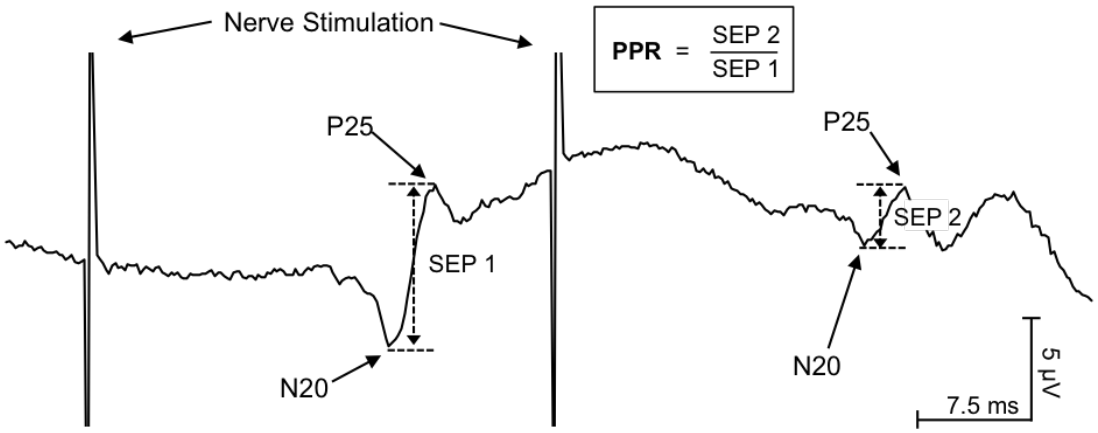

Figure 2.2 Sample averaged somatosensory evoked potential trace showing the first and second N20-P25 waveforms.

Ragert and colleagues show that at an inter-stimulus interval of 30 ms, the amplitude of N20-P25 following the second pulse is consistently reduced when compared to the N20-P25 amplitude immediately following the first pulse[4]. As this inter-stimulus interval (ISI) increases, the degree of suppression decreases, such that the paired pulse N20-P25 is similar in amplitude to that of the initial pulse[39]. Intensity of peripheral stimulation has been shown to have a large effect on the degree of PPR with higher intensities resulting in greater inhibition of both the N20-P25 and the N20 alone[36-38, 40]. The physiological mechanisms that mediate PPR remain unclear. However, one concept that may underpin PPR is called in-field inhibition. In-field inhibition involves the excitation of a neuronal population that persists for ~ 25 ms that is subsequently truncated by latent inhibition within the same neuronal population. Therefore, the greater the excitation of the neuronal population, the greater the resulting in-field inhibition[41-43].

2.1.4 Tactile Perception

The ability to perceive touch on the hand can be attributed to four main types of receptors: Meissner corpuscles, Pacinian corpuscles, Merkel cells and Ruffini endings. These mechanoreceptors are dense within the glabrous skin of the finger digits. Meissner corpuscles and Merkel cells are located superficially and are innervated by Type I fast adapting and slow-adapting afferent nerve fibers, respectively. Slow Type I fibers primarily respond to the distinct edges of objects, where fast Type I fibers respond to movement[14,42]. Ruffini endings are innervated by slow-adapting Type II afferents that respond to stretch and low-frequency vibration and Pacinian corpuscles are innervated by fast-adapting Type II afferents that respond to high-frequency (30-500Hz) vibration[14,42]. Both are located deep within the skin.

Tactile perception is our ability to perceive tactile events that occur both in space (i.e. spatial) and in time (i.e. temporal). It can be measured in terms of a person's ability to distinguish between a single stimulus or two distinct stimuli and is referred to as temporal discrimination (TD). Typical thresholds for TD range from approximately 30-50 ms in healthy adults[43]. With disorders such as focal hand dystonia where somatosensory perception is impaired, TD thresholds increase to 100-155ms[44–46]. Tasks involving TD have been shown to activate multiple brain regions including: supplementary motor area, anterior cingulate and right postcentral gyrus[43] however deficits are the greatest in those with lesions to SI[47]. A similar measure of tactile perception has been studied using TOJ, which probes the ability to detect where the earlier of two closely timed stimuli occurred across two cutaneous locations. Typical thresholds for TOJ in controls range from 20-40

ms[48,49]. Further, studies have investigated the effects of attention[50–52], spatial location[53] and multisensory stimuli on TOJ[54–56] demonstrating that experimental parameters have a large influence on TOJ thresholds.

2.2 Techniques in Transcranial Magnetic Stimulation

2.2.1 Introduction

Transcranial Magnetic Stimulation (TMS) is a form of non-invasive magnetic stimulation used to excite cortical neurons. TMS operates via induction of a magnetic field generated from an electrical current which runs through the coil[57]. This field reaches a maximum of 2 Tesla and is partly determined by the shape of the coil used. A figure-of-eight (or butterfly) style is a uniquely designed coil that produces a localized current between the coil's two loops[57,58]. Indirect waves are produced as a result of transsynaptic activation of the pyramidal neurons which synapse with and activate corticospinal neurons[59]. Following the activation of corticospinal neurons, the depolarizing volleys travel toward the alpha motorneuron in the spinal cord where they form an excitatory post synaptic potential (EPSP). An EPSP of an adequate size will result in depolarization and generation of an action potential which subsequently results in a motor response[60]. Coil orientation with respect to the mid-sagittal plane is an important consideration as this will affect the direction of induced current. The largest motor evoked potentials (MEPs) are obtained when the direction of current flows in the posterior-to-anterior direction; this orientation produces I waves at a low intensity[57].

2.2.2 Theta Burst Stimulation

A repetitive form of TMS, TBS utilizes high frequency trains of pulses to induce LTP or LTD-like effects in the cortex. LTP occurs when thresholds for calcium (Ca^{2+}) are increased resulting in an influx of Ca^{2+} into the cell where as LTD occurs when Ca^{2+}

thresholds are decreased resulting in a net efflux out of the cell[61–64]. TBS has been employed using one of two protocols: iTBS or cTBS (Shown in Figure 2.3). Both iTBS and cTBS involve bursts of 3 pulses at a frequency typically either 50 Hz[3,7,65–67] or 30 Hz[8–10,68]. These 3 pulse bursts repeat in a train of bursts at an inter-burst frequency of either 5 Hz[65] or 6 Hz[8] for a total of 600 pulses. During iTBS this train of pulses is non-continuous, lasting for 2s at a time, followed by a period of no pulses and repeated after 10s[65]. Typical iTBS lasts for a total of 190s. During cTBS the train of pulses is uninterrupted and lasts for a total of 40s[65].

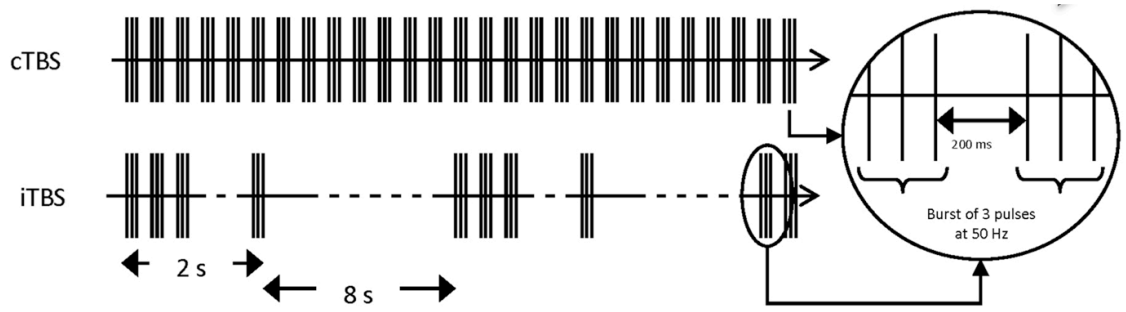

Figure 2.3 Schematic of original TBS protocols: cTBS and iTBS proposed by Huang et al., 2005. Figure modified from Oberman et al., 2010[69].

In rats receiving TBS, isoforms of the enzyme responsible for production of inhibitory neurotransmitter γ-aminobutyric acid (GABA) respond differently than to low-frequency rTMS[70]. Isoform glutamic acid decarboxylase (GAD) 67 decreases in concentration within SI inhibitory interneurons whereas GAD 65 and GABA-transporter 1 (GAT-1) increases in concentration, with iTBS having the strongest influence[70]. These changes last for a period of two hours before reversal of the effects occurs, resulting in a greater

concentration of GAD 67 and lesser concentrations of GAD 65 and GAT-1[70]. These effects were seen to last as long as seven days. In studying the inhibitory interneurons that synapse on pyramidal cells, recent research suggests that iTBS and cTBS may act differently on specific types of inhibitory cells[71]. ITBS has been shown to have a particular influence over cells that express the protein parvalbumin (PV) and cTBS specifically modulates cells that express the protein calbindin D-28k (CB)[71]. In humans, TBS-induced plasticity is limited to a much shorter time period, nonetheless multiple studies have shown a propensity for plasticity in SI with iTBS inducing LTP-like effects for a period of up to 30 minutes[1–4] and cTBS inducing LTD-like effects to a maximum of 45 minutes after application of a 30 or 50 Hz TBS protocol[7,9,10].

2.3 Plasticity Studies in Somatosensory Cortex

2.3.1 Effects on Motor Evoked Potentials

SI has been shown to have extensive cortical projections to surrounding regions. TBS protocols have been employed over SI as a means of studying the effect on excitability in surrounding regions of the brain, namely M1. Following application of 50 Hz cTBS or iTBS over SI, Katayama *et al*. saw no change in MEP amplitude at intervals ranging from 0 to 45 minutes post protocol in the left abductor pollicis brevis (APB) muscle[3]. These results support previous findings that 50 Hz cTBS delivered to a site 2 cm posterior to M1 (most likely corresponding to SI) results in no significant change in MEP size measured in first dorsal interosseous (FDI) muscle[7]. However when delivered at the same intensity of 80% active motor threshold (AMT), TBS has been shown to produce facilitation of MEPs when the coil is oriented only in the anterior-to-posterior (AP)-

posterior-to-anterior (PA) direction[10]. Further work from our lab shows that the application of a modified 30 Hz cTBS protocol over SI, produces lasting facilitation of MEPs for 45 minutes post protocol[9].

2.3.2 Effects on Somatosensory Evoked Potentials

A wider range of literature exists looking at the effects of TBS over SI on the excitability of SI itself as opposed to its effects on M1. As discussed, SI excitability is most commonly studied through SEPs. ITBS delivered at a frequency of 50 Hz has been shown to facilitate the SEP N20-P25 amplitude[2] as well as the N20 alone for as long as 30 minutes when applied over SI[1,3]. ITBS has also been shown to substantially suppress the degree of paired-pulse inhibition of the SEP N20-P25 component[4]. 50 Hz cTBS applied over SI results in changes in the SEP waveform, however not in the N20 or N20-P25 components, presumed to originate from Brodmann area 3b[7,36]. Rather, the SEP P25-N33 component, thought to originate in more superficial area 1 was suppressed[7,72]. To date, 30 Hz iTBS and cTBS protocols have not been used to investigate SI excitability in the form of SEPs.

2.3.3 Effects on Tactile Perception

While there is much literature on alterations in tactile perception after low[73–75] and high-frequency[76–79] rTMS, only a handful of studies have studied this following the application of TBS to SI. Ragert and colleagues show that after iTBS over SI, the thresholds for two-point discrimination are significantly lowered, thus allowing for increased accuracy[4]. This effect was tested only at 10 minutes following application of iTBS. Decreases in

performance were seen by Conte and colleagues, when subjects were tested on a somatosensory temporal discrimination threshold (TDT) task following cTBS[80]. Changes were recorded at 5 and 15 minutes post TBS. Supporting results were seen with subjects showing increased TDT following cTBS for a period lasting 18 minutes post protocol[11]. Similar increases in thresholds were seen in performance on a similar spatial discrimination task. Interestingly, these increases in thresholds are not evident during TOJ following cTBS, where the participant is required to determine the order in which two stimuli are presented[12].

2.4 Studies in Metaplasticity

Homeostatic metaplasticity is based on the theory proposed by Bienenstock, Cooper and Munro stating that synaptic plasticity is bidirectional and at any point can move toward LTP or LTD, depending on the previous state of the postsynaptic neuron[81] (Figure 2.4).

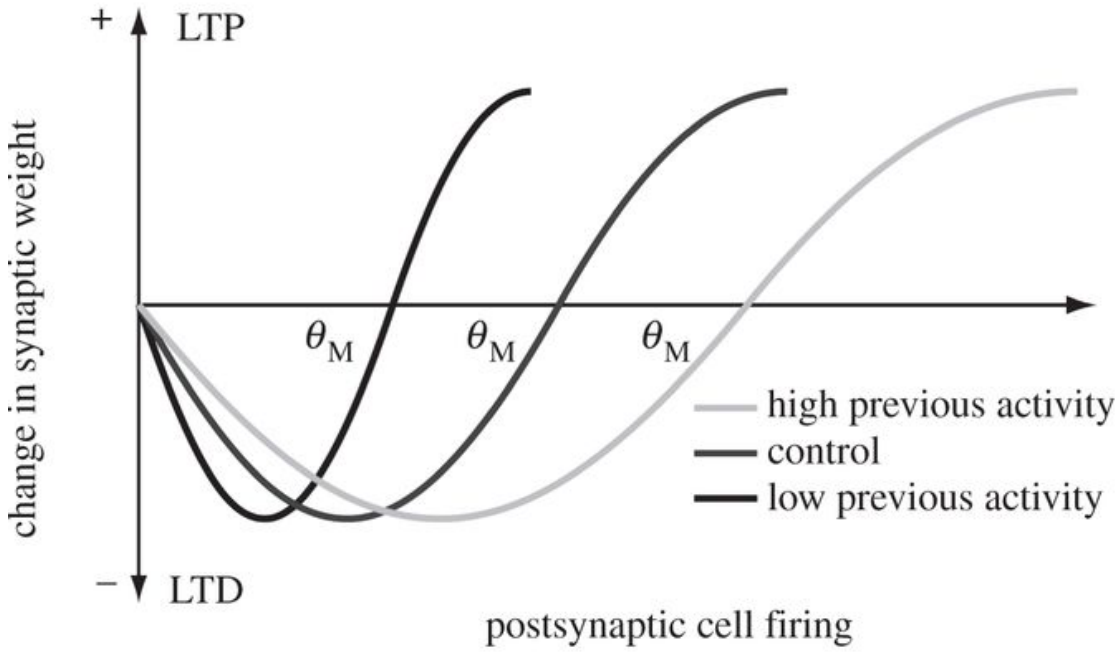

Figure 2.4 BCM Model for homeostatic metaplasticity depicting how low previous activity of the cell causes the threshold for LTP induction to decrease and conversely, at high previous levels of postsynaptic activity, the threshold for LTP induction increases. Figure modified from Hulme et al., 2014[82].

TMS studies in metaplasticity involve priming a plasticity inducing protocol with another form of plasticity inducing TMS. To date, metaplasticity has primarily been studied in M1. When 1 Hz rTMS is primed with 10 minutes of either anodal or cathodal transcranial direct current stimulation (tDCS), MEP amplitude recorded from the contralateral FDI decreases or increases, respectively[83]. Metaplasticity studies in SI are limited to either

paired associative stimulation (PAS) or 5 Hz rTMS. Bliem and colleagues discovered that priming peripheral high-frequency stimulation (pHFS) with paired associative stimulation $(PAS)_{N20\text{-}15}$ resulted in facilitation of SEP N20 and N20-P25 amplitudes and a decrease in tactile discrimination threshold[84]. Conversely, priming with $PAS_{N20\text{-}2.5}$ resulted in inhibition of SEP N20 and N20-P25 amplitudes and an increase in tactile discrimination threshold. In a similar study, pHFS was primed instead with 5 Hz rTMS and resulted in a suppression of the SEP effects seen when pHFS was delivered alone[39].

Recent studies have looked at priming TBS protocols with various types of TMS. RTMS appears to be an ineffective method of TBS priming; when cTBS was primed with either 2 or 6 Hz rTMS, there was no change to the effect produced by delivering cTBS on its own[85]. Rather, priming TBS protocols with either an identical or opposite form of TBS typically produces lasting changes in cortical excitability. Multiple groups have demonstrated that priming cTBS with iTBS results in a further suppression of MEPs beyond that seen when cTBS is delivered alone[85–87]. Further, when cTBS was primed with an identical cTBS protocol, MEP amplitude was significantly suppressed for a period reaching up to two hours[13]. In combining multiple variations of TBS over M1, Murakami and colleagues show a general trend for TBS metaplasticity:

a. When a test TBS protocol is primed with an identical protocol, the normal effects of the test protocol are suppressed.
b. When a test TBS protocol is primed with an opposite protocol, the normal effects of the test protocol are facilitated[87].

To date, the above studies have provided us with details on the nature of TBS-induced metaplasticity within M1, however no such studies have investigated similar effects within SI.

Chapter 3: Investigating Metaplasticity in Somatosensory Cortex

3.1 Introduction

Plasticity is itself regulated by the mechanisms of plasticity, an effect termed metaplasticity whereby synaptic activity influences the direction and amplitude of forthcoming plasticity at those synapses[88]. At a given synapse, LTP increases the threshold for Ca^{2+} entry thereby promoting the subsequent induction of LTD[81,88–90]. In contrast, LTD at a synapse will decrease the Ca^{2+} threshold and therefore promote subsequent LTP[88,90]. Metaplasticity is proposed to perform an essential function of limiting excess LTP and/or LTD that may otherwise damage cells[90] and simultaneously balance the levels of excitation and inhibition to allow for relevant synaptic plasticity [87,90].

In humans, Transcranial magnetic stimulation (TMS) plasticity protocols such as Theta-burst stimulation (TBS) induce plasticity and metaplasticity within primary motor cortex (M1) such that exposure to one protocol facilitates or depresses neural responses to subsequent stimulation[5,13,85–87,91,92]. TBS delivered in continuous (cTBS) and intermittent (iTBS) patterns may evoke opposite effects such that the amplitude of the TMS-elicited MEP is decreased[7–9,65–68] and increased[65,67] respectively, although these relationships are complicated by the stimulation parameters and individual differences and may not always occur[8,68,93,94]. When identical TBS protocols are applied consecutively over M1, responses are reversed such that cTBS followed by cTBS evokes LTP-like increases in MEP amplitude[13,91] while iTBS followed by iTBS evokes LTD-like decreases[91,92]. Metaplasticity may therefore participate in human M1 by preserving the balance of

excitation and inhibition and limiting excessive plasticity in either direction.

It is unclear whether metaplasticity principles derived from study of human M1 apply to neighboring SI. Electrophysiology and neurochemical studies in rat SI indicate that both cTBS and iTBS increase the amplitude of SEPs, and decrease the number of cells containing PV and CB calcium binding proteins[71,95,96]. Collectively, these data indicate a TBS-induced reduction in inhibitory circuits within SI and are suggested to be mediated via LTD at PV- and CB-expressing cells that, in turn, disinhibit pyramidal cell output. Further, the effects of cTBS and to a greater extent iTBS are reduced in rats which subsequently learn a tactile discrimination task, indicating complex metaplasticity interactions within SI[97].

In humans, iTBS and cTBS over SI have been shown to increase, decrease or not change the amplitude of SEP components[1–4,7,98]. Measures of tactile perception reveal cTBS-induced impairments in both spatial[11] and temporal acuity[11,12]. To date, there are few studies in humans that examine TBS-induced effects on SI physiology and touch perception[4] and there are no studies that investigate whether SI demonstrates TBS-induced metaplasticity. The present study examined the physiological and psychophysical consequences of both single and paired TBS protocols. I specifically compared a single protocol of cTBS and iTBS to investigate their similarities and differences. Further, I compare the effects of a single versus double TBS protocol to investigate metaplasticity effects. Our data indicate that cTBS and iTBS have similar effects such that measures of intracortical inhibition and touch perception are altered

without changes to the first N20-P25 SEP. These data are similar to that observed following intermittent high-frequency stimulation such that SEP (using paired-nerve stimulation) increased but with no change in excitation measured by SEP 1[99], and TBS-induced effects on tactile temporal perception[12]. Further, consecutive, identical TBS protocols lead to metaplasticity in tactile perception only, suggesting that metaplasticity operates via changes in intracortical inhibition rather than changes in excitatory mechanisms within SI.

3.2 Methods

Participants

Sixteen healthy adults participated (6 females, mean age = 23 ± 5.2 years). All participants were right-handed and were screened using a modified version of the Edinburgh Handedness Scale[100]. The main experiment required participation in six sessions separated by a minimum of 1 week. All sessions were held at approximately the same time of day in order to minimize cortisol-related excitability changes that may occur throughout the day[101,102]. All subjects provided written informed consent prior to participation. The study was approved by the McMaster Research Ethics Board and conformed to the Declaration of Helsinki.

Electromyography (EMG) recording

Electromyography was recorded using surface electrodes (9mm diameter Ag-AgCl) placed over the bilateral abductor pollicis brevis (APB) muscle and the first dorsal interosseous (FDI) muscle in a belly tendon montage. Right APB was the target muscle

for the M1 hotspot used for obtaining motor threshold as described below. The purpose of recording EMG over right FDI and left APB and FDI was to ensure neighboring muscles were relaxed during testing. EMG signals were band-passed filtered between 20 Hz and 2.5 kHz, amplified 1000× (Intronix Technologies Corporation Model 2024F with Signal Conditioning; Intronix Technologies Corporation, Bolton, Canada) and digitized at 5 kHz by an analog- to-digital interface (Power1401; Cambridge Electronics Design, Cambridge, UK). All EMG data was collected using Signal software v 6.02, Cambridge Electronic Design Limited, Cambridge, UK).

Transcranial magnetic stimulation and Neuronavigation

Single pulse TMS was applied over left M1 using a 70 mm inner diameter figure-of-eight air cooled coil attached to a Magstim Super Rapid^2 Stimulator (Magstim, Whitland, UK). The coil was oriented at a 45° angle to the mid-sagittal line to induce a posterior-to-anterior current in M1. The motor hotspot was identified as the optimal site for eliciting a consistent MEP in the relaxed, right APB muscle and was digitally marked using Brainsight Neuronavigation Software (Rogue Research, Montreal, Canada). Resting motor threshold (RMT) was obtained at the motor hotspot and defined as the minimum stimulation intensity required to elicit MEPs > 50 μV in 5 out of 10 consecutive trials[103]. TBS was delivered to SI at the location of the C3' electrode as defined by the International 10-20 System. This location was digitally marked for each participant in order to maintain the same coil placement between sessions. CTBS was delivered at a frequency of 30 Hz with bursts of 3 pulses repeating at 6 Hz for a total of 612 pulses (~ 40 s)[8]. ITBS was delivered at 30 Hz and consisted of a 2 second train of 3 pulse bursts (6

Hz burst frequency) repeated at 10 second intervals for a total of 612 pulses (~190 s) (modified from[65]). TBS at 30 Hz was selected since it has been shown to produce a reduced inter-individual variability[8–10,68]. All TBS protocols were applied at an intensity of 70% RMT as opposed to AMT to avoid contraction prior to TBS which can itself elicit metaplasticity[13,93].

Somatosensory Evoked Potentials & Paired Pulse Ratio

EEG was recorded from SI using the International 10-20 System with the active electrode placed at C3' and referenced to Fz[104]. A ground electrode was placed over the left clavicle. Signals were band-passed filtered between 2 Hz and 2.5 kHz, amplified 10000 × (Intronix Technologies Corporation Model 2024F with Signal Conditioning; Intronix Technologies Corporation, Bolton, Canada) and digitized at 5 kHz by an analog- to-digital interface (Power1401; Cambridge Electronics Design, Cambridge, UK). The active EEG lead was removed during application of TBS and was replaced immediately following TBS. To ensure accurate replacement, the location of C3' was digitally marked using Brainsight as well as with a non-permanent marker directly on the scalp. Electrode impedance was tested before and at each time-block after TBS to maintain a level <5 kΩ (UFI Checktrode, Model 1089 Mk III, UFI, Morro Bay, USA). The median nerve at the wrist was stimulated with a bar electrode at 1 Hz with pairs of pulses (each 200 μs, 30 ms inter-stimulus interval) (DS7A, Digitimer Research Instruments, Hertfordshire, UK). In this way, changes in SI excitability were assessed via the amplitude of the first N20-P25 (SEP 1) and changes in SI intracortical inhibition were assessed via the amplitude of the second N20-P25 (SEP 2) that is inhibited relative to SEP 1, and also the ratio of SEP

2/SEP1 amplitude (i.e. the paired-pulse ration (PPR)). The intensity for nerve stimulation was set at motor threshold defined as the minimum intensity required to evoke a visible twitch in the APB muscle. A total of 500 pulse pairs were delivered for each time-block (described below).

Temporal order judgment (TOJ)

TOJ was assessed using the Cortical Metrics device version 6.0 (Cortical Metrics, North Carolina, U.S.A, see Figure 3.1A). The right hand was placed on the device with each digit positioned in the individual finger grooves. The task delivered vibrotactile stimulation (1000 ms, 25 Hz, 300 μm) to the volar pad of digits 2 and 3 separated by an interstimulus interval (ISI) that was defined by the ongoing performance. The first trial always began with the ISI set at 150 ms. Participants were queried to report the identity of the digit that received the first stimulus. A correct response resulted in a shortening of the ISI by 5% (i.e. the task becomes more difficult) and an incorrect response resulted in an increase in the ISI by 5% (i.e. task becomes easier). Thirty-one total trials were performed in each time block and the order of digit presentation (i.e. digit 2 or digit 3) was randomized across trials. No visual or auditory feedback was provided to participants during or following the TOJ task. Prior to testing in each time block, participants were (re)acquainted with the task, completing three practice trials wherein visual feedback was provided. In the case where a trial was answered incorrectly, the participant would repeat all three trials until all stimuli were correctly identified.

Experiment timeline

Each experimental session consisted of a single or two consecutive TBS protocols (Figure 3.1B). The order of TBS protocol delivery was pseudo-randomized across participants. Measurements were collected prior to TBS (T0), and following TBS at 5 mins (T1), 25 mins (T2), 50 mins (T3) and 90 mins (T4). The order of SEPs and TOJ collections were counterbalanced across participants. A fifteen minute wait time was imposed following the collection of the T0 data and prior to the delivery of the first TBS. A fifteen minute time window elapsed between the deliveries of consecutive TBS protocols in order to deliver the second TBS protocol at the point when the effects of the first have been shown to reach their maximum[65,93,105]. Importantly, dependent measures were not acquired between the delivery of consecutive TBS protocols. This is an important consideration since the dependent measures themselves may interfere with the metaplastic effects of TBS. Participants wore earplugs (29 dB) and sat upright with their eyes closed and head and neck supported in a headrest during acquisition of all dependent measures.

3.3 Data Analysis

The peak-to-peak amplitude of SEP 1 and SEP 2 were calculated from the time-locked average of up to 500 trials for each individual at each time block. Trials were not included in the average if they contained excessive noise or eye-blink artifacts. The amplitude of SEP 1 was determined to be the peak-to-peak amplitude between the negative N20 minimum and the positive P25 peak. SEP 2 was measured as the peak-to-peak amplitude based on the latencies of the N20 and P25 of SEP 1, plus an additional 30

ms added to each to account for the time interval between the first and second peripheral nerve stimulus. PPR was calculated as the peak-to-peak amplitude of SEP 2 divided by the peak-to-peak amplitude of SEP 1[106] (Figure 3.1C). TOJ threshold was defined as the ISI of the last trial in each time block. Statistical analyses were performed as follows. First, an outlier analysis was performed using data for all interventions at T0 (baseline) using SPSS and individuals were removed from an intervention when their T0 data was deemed to be an outlier for that intervention. Analyses were performed on normalized data (i.e. T1/T0) when T0 data were statistically different between interventions. A two-way repeated measures analysis of variance (ANOVAs) on normalized data using within subject-factors TIME (4 levels; T1, T2, T3, T4) and INTERVENTION (6 levels; cTBS, iTBS, cTBS-cTBS, iTBS-iTBS, cTBS-iTBS, iTBS-cTBS) compared all interventions. Subsequent two-way ANOVAs were performed using within subject factors TIME and INTERVENTION to compare 1) iTBS versus cTBS, and 2) metaplasticity via identical protocols (cTBS vs. cTBS-cTBS; iTBS vs. iTBS-iTBS) to test for metaplasticity for that given protocol. In the event that data did not meet the assumption of sphericity, the Greenhouse-Geisser method was used to correct the *p*-value. Post Hoc Tukey's tests were used to further investigate significant differences. Significance was set at $p < 0.05$.

3.4 Results

Following outlier analysis at T0, the following data were removed. For SEP 1, participant 2 was removed from cTBS-cTBS. For SEP 2 and PPR, participants 2 and 11 were removed from cTBS-cTBS, and participant 2 from cTBS, iTBS and iTBS-iTBS. For TOJ,

participants 6 and 16 were removed from cTBS. The group-averaged RMT was 62.3% ± 10.6% of maximum stimulator output (MSO) and was not different across interventions ($F_{(5,95)}$= 0.12, p = 0.99, cTBS = 60.9%, iTBS = 63.0%, cTBS-cTBS = 61.4%, iTBS-iTBS = 62.4%, cTBS-iTBS = 62.5%, iTBS-cTBS = 63.4%). Similarly, the TBS intensity was not different between interventions ($F_{(5,95)}$ = 0.15, p = 0.98, cTBS = 42.6%, iTBS = 44.3%, cTBS-cTBS = 43.0%, iTBS-iTBS = 43.9%, cTBS-iTBS = 43.9%, iTBS-cTBS = 44.5%). Table 3.1 displays the results of all statistical analyses. Two-way ANOVA examining all protocols revealed an effect of TIME without an INTERVENTION effect or interaction. Table 3.2 displays all group-averaged means and standard deviations for each intervention at each time block for each dependent measure.

CTBS versus iTBS

The effects of cTBS and iTBS were similar for all measures of physiology and perception. For SEP 2, the main effect of TIME revealed that cTBS and iTBS increase the amplitude at T3 (50 min) (Figure 3.2B) without changing SEP 1 (Figures 3.2A & C). For PPR the main effect of TIME did not reveal differences between time blocks. Further, for TOJ thresholds, the main effect of TIME revealed decrements in performance at T2 (25 min) by ~ 15% for cTBS and ~20 % for iTBS (Figure 3.2D). Figure 3.2E plots the group-averaged TOJ performance averaged over iTBS and cTBS as function of trial number. The decrement in in TOJ performance emerges as performance approaches threshold (trials 25-31) and is not observed at suprathreshold levels (trials < 27). These data indicate that 30 Hz cTBS and iTBS exert similar effects on SI physiology and TOJ performance.

Metaplasticity within SI

Figure 3.3 displays the group-averaged physiology and psychophysical data investigating metaplasticity effects of cTBS. No differences were observed between cTBS and cTBS-cTBS for SEP 1, PPR and SEP 2. For TOJ, there was a significant effect of INTERVENTION (Table 1) indicating that thresholds were significantly elevated following cTBS versus cTBS-cTBS across all levels of time. The size of the main effect was ~ medium strength as calculated by Cohen's d (0.62). Further, the cTBS-cTBS protocol demonstrated a trend towards improvements in TOJ performance at T4 (Figure 3.3D) an effect observed in 10 out of 14 individuals (solid black lines, Figure 3.3E). In summary, these data indicate that cTBS-cTBS demonstrates metaplasticity for the dependent measure of TOJ.

Figure 3.4 plots the group-averaged data investigating the metaplasticity effects of iTBS. Metaplasticity effects were not observed for measures of SEP 1, SEP 2 (showing facilitation at T4) or PPR (Figures 3.3A-C). Evidence of metaplasticity was observed for TOJ with a significant interaction at T3 (50 min) whereby TOJ thresholds were elevated following iTBS-iTBS compared to iTBS (Cohen's d = 0.381, 'small') (Figure 3.3D). Further, both protocols induced significant decrements in performance with 'medium' effect sizes (iTBS at T2, Cohen's d = 0.440 and iTBS-iTBS at T3, Cohen's d= 0.422) (Table 1)(Figure 3.3E). These data indicate that iTBS protocols induce metaplasticity with effects that vary over time rather than by direction of changes.

Metaplasticity was not further investigated in cTBS-iTBS and iTBS-cTBS protocols.

Since the TBS plasticity protocols revealed similar effects, I was unable to examine the effects of pairing protocols with opposite effects.

3.5 Discussion

Three novel findings were revealed. First, cTBS and iTBS over SI yield similar effects on physiology and perception. Second, cTBS and iTBS-induced metaplasticity is observed for measures of tactile perception but not physiology. Third, the metaplasticity effects of cTBS and iTBS differ with respect to the direction and time course of induced changes. These data suggest that metaplasticity effects of consecutive iTBS and cTBS protocols may promote homeostatic changes within and between cortical columns, likely via modulation of inhibitory circuits.

CTBS and iTBS modulate SI physiology and perception similarly

Our findings indicate that cTBS and iTBS increase the amplitude of SEP 2 (23.5% and 15.2%, respectively) and do not significantly alter SEP 1. These effects emerge at 25 minutes (T2) and maximal effects occur in the time range of 25-50 (for cTBS) and 90 minutes (for iTBS). This finding is consistent with previous literature that shows the time course of effects to be between 15-30 minutes following TBS over SI[1–3]. Compared to SEP 1, SEP 2 is reduced in amplitude[107] and is considered a consequence of GABAergic inhibition acting within SI[39,108–113]. I observed marginal reductions in PPR for iTBS and cTBS, in support of the marginal iTBS- induced suppression in PPR observed by Ragert and colleagues[4]. However, I note that the magnitude of PPR reflects changes in SI intracortical inhibition when fluctuations in SEP 1 and SEP 2 are disproportionate and/or

divergent. Collectively, the data suggest that TBS targets inhibition within SI. Evidence is derived from the observation that late somatosensory high-frequency oscillations are suppressed following cTBS, oscillations that are thought to be generated by GABAergic inhibitory interneurons[3]. Further, cTBS over M1 suppresses short-interval intracortical inhibition mediated via $GABA_A$ receptors[65]. Last, our observation that SEP 1 is unchanged following TBS, suggests that TBS is not creating obvious changes in the excitatory circuitry within SI that generates the first SEP.

CTBS and iTBS impaired the ability to perform TOJ (at ~15% and 20%, respectively) at ~25 minutes following stimulation. A similar decrement in TOJ (~18%) follows 50 Hz cTBS[12] with even larger performance changes for other measures of tactile acuity[11]. The data indicates that 30 Hz TBS protocols, which I suggest reduce inhibition within SI, likely alter TOJ by reducing the lateral inhibition necessary to create the spatial contrast between the cortical columns receiving inputs from digit 2 from those receiving inputs from digit 3. Figure 3.5 provides a schematic of the predicted effects of metaplasticity in SI using a model derived from TBS research in rat species. The reduction in lateral inhibition is likely accompanied by a reduction in the level of recurrent inhibition on the pyramidal cells (as evidenced by increased SEP 2), and their combined effect may further reduce the spatial distinction between digits 2 and 3 making TOJ more challenging under these circumstances. Some evidence is derived from studies in individuals with Autism who demonstrate impaired TOJ[114]. Autism is associated with alterations in GABAergic inhibition (e.g. [115–117]).

Metaplasticity via homogenous TBS protocols

A fundamental comparison in this study was the evaluation of homogeneous metaplasticity in SI. In both instances (cTBS versus cTBS-cTBS and iTBS versus iTBS-iTBS) metaplasticity was observed in measures of TOJ. The impairment in TOJ following a single cTBS protocol was abolished following cTBS-cTBS and trended towards an improvement in performance occurring at 90 minutes (T4). These data suggest that cTBS-induced metaplasticity effects have the potential to improve tactile perceptual capabilities. SEP 1, SEP 2 and PPR were not statistically different than the effect of a single cTBS protocol. Therefore, metaplastic effects of the second cTBS protocol appear to restore the excitability at interneurons responsible for TOJ only across all levels of time.

The iTBS versus iTBS-iTBS comparison presented similar, yet distinct results. In this case, metaplasticity is a time-based effect whereby perceptual impairments via iTBS at 25 minutes occur later in time (~50 mins) following iTBS-iTBS. At T2 the metaplastic effects appear to be directional whereby the tactile performance decrements following iTBS are brought back towards baseline levels following successive iTBS protocols. At T3 there also appears to be a directional metaplastic effect whereby near baseline levels of tactile performance following iTBS instead produce impairments following iTBS-iTBS. Therefore metaplasticity is demonstrated in both directional changes that reverse over the time course of the TBS-induced metaplasticity.

CTBS and iTBS-induced metaplasticity produce different effects despite having similar

responses when delivered as single protocols. Metaplasticity therefore allows us to uncover underlying changes that cannot be seen following the delivery of a single protocol and only become apparent following the delivery of the homogeneous metaplastic protocol. For example, since cTBS and iTBS both produce similar reductions in cortical inhibition shown by an increased SEP 2 and impairments in tactile acuity, one might make the assumption that the reduction in inhibition seen in SEP 2 contributes to the tactile performance decrements. However their metaplastic effects show changes only in TOJ. From this we can conclude that while cTBS and iTBS similarly affect inhibition, they likely do so at different sites and/or relative strengths, thus producing differences apparent upon applying two protocols in succession.

Comparison to previous literature

Our data reveals that TBS manipulates tactile perception and intracortical inhibition but not excitation associated with the first SEP 1. A study investigating metaplasticity within SI using intermittent high-frequency tactile stimulation (iHFS) primed with 5Hz rTMS yielded similar results[99]. In their work primed iHFS produced reductions in overall inhibition as measured by an increase in PPR and in SEP 2 with no changes in SEP 1. Tactile acuity measured by 2-point discrimination was improved. There are notable differences in the methodology between the above study and ours namely the plasticity-inducing protocols (TBS versus 5Hz rTMS) and the tactile task. However, collectively, these two studies converge on the findings that TMS–induced changes target the same neuronal populations that mediate cortical inhibition.

I tested the combination of cTBS and iTBS delivered in succession with its non-identical

TBS to examine whether the effect of either would be amplified in terms of its amplitude or duration of effects. Over M1, cTBS-iTBS lead to greater enhancement of MEP amplitude than did iTBS alone[87]. In the reverse scenario however, iTBS-cTBS lead to no change compared to the effects of cTBS alone. Our data did not show this trend, and this may be a result of increased variability generally seen within the primed TBS protocols compared to the unprimed protocols. Another possible explanation for these differences is the fact that cTBS did not operate to reduce SI excitability as it did in the aforementioned study focused on M1.

Methodological Considerations

Altering the timing between two consecutive TBS protocols has been demonstrated to yield very different effects on cortical physiology[87,91,92]. Therefore, our choice of an interval of 15 minutes is consistent with the timing needed to reverse effects seen with cTBS and iTBS[87]. I opted to use a 30 Hz TBS protocol to reduce the inter-subject variability associated with TBS delivery over M1[8]. However, simulations have demonstrated that reducing the frequency of TBS may promote the induction of depression[94]. Therefore, iTBS at 30 Hz may have enhanced the opportunity to observe depressive effects, which may have contributed to similar effects of the two protocols. Pseudo-randomizing the order of interventions was implemented to eliminate possible carry-over effects. Finally, I did not collect SEP or psychophysical data in the 15 minute interval between consecutive TBS protocols. This was an important consideration to avoid contamination or contribution of the dependent measures to the effects of metaplasticity.

3.6 Conclusion

The data indicate a similarity in the effects of cTBS and iTBS on SI physiology and tactile perception. Metaplasticity is observed as a change in the TOJ-induced impairments following cTBS-cTBS and iTBS-iTBS. The data also suggests that cTBS and iTBS operate differently in their metaplasticity effects, with changes in perception occurring as a reversal of effects after cTBS-cTBS and a modification of the time course of changes seen in iTBS-iTBS. In particular, the metaplasticity effect of consecutive cTBS protocols may provide one opportunity to improve tactile perception and is a fundamental point of progress that has wide-ranging clinical applications such as stroke, dystonia, Autism, spinal cord injury and Parkinson's disease.

3.7 Tables and Figures

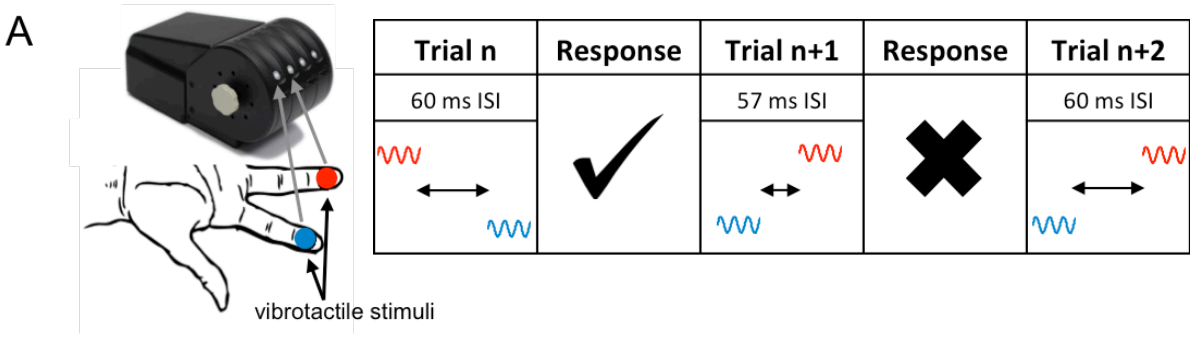

Figure 3.1: Experiment Protocol

Figure 3.1: Experiment Protocol. A) Depiction of the methods for the TOJ task. A vibrotactile stimulator (Cortical Metrics) was used and stimulation was applied to the palmar surface of digits 2 and 3 (blue and red respectively). The amplitude of the two stimulations was 300 μm and the ISI between the two stimulations started at 150 ms. Upon successful indication to which finger the stimulation was applied to first the ISI would reduce by 5% of the previous trial. If the participant did not answer correctly the ISI would increase to the previous ISI. Thirty-one total trials were collected and the average of the last trial (trial 31) was determined as the TOJ threshold or the minimum ISI that the order of two stimulations can be judged. **B)** Depiction of the experiment timeline. Time blocks are labeled at the top with the dependent measures within the boxes. T0 indicates baseline measurements. Upon completing the baseline measurements 15 minutes elapsed before the experiment intervention as depicted by the arrow. 6 sessions were completed on different days of either plasticity protocols using cTBS (grey) or iTBS (black) or metaplasticity protocols using combinations of cTBS and iTBS. The amount of time elapsed between the experimental intervention to when the post measurement blocks started are as follows: 5, 25, 50 and 90 minutes. Post measurements at each time block were completed in an average of 15 minutes and are compared to the baseline (effect of time) or between interventions (effect of intervention). **C)** Depiction of an average SEP trace from one participant. SEP 1 was calculated as the N20-P25 amplitude after the first stimulation and SEP 2 was calculated as the N20-P25 amplitude after the second stimulation. PPR was calculated as (SEP 2)/(SEP 1).

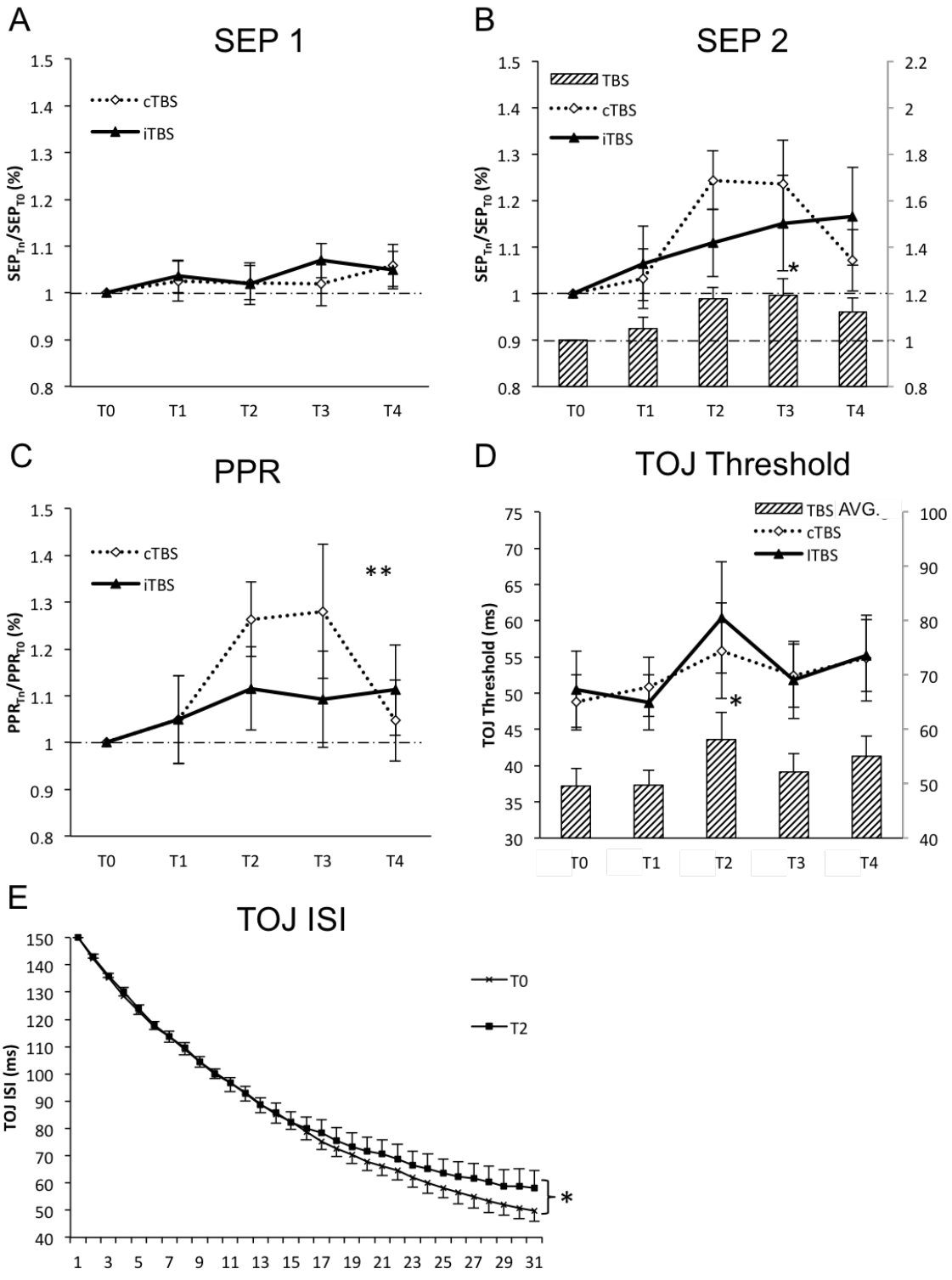

Figure 3.2: Plasticity Effects of cTBS versus iTBS

Figure 3.2: Plasticity Effects of cTBS versus iTBS. All data for SEP 1, SEP 2 and PPR was normalized at each post time block to the baseline measurement T0 except for TOJ where T0s were not statistically different. Values above the horizontal dashed line correspond to an increase in the amplitude (SEP 1 and SEP 2) or reduction in the PPR compared to baseline values. **A)** Group-averaged SEP 1 means and standard error of the mean (N=16). No significant increases were seen. **B)** Group-averaged SEP 2 means and standard error of the mean (N=15). Histogram depicts the main effect of TIME (average of cTBS and iTBS means and standard error of the mean; a significant increase in SEP 2 amplitude is seen at T3. **C)** Group-averaged PPR means and standard error of the mean (N=15). Although a significant effect of TIME was seen, Tukey's post-hoc revealed no significant time differences **D)** Group-averaged TOJ means and standard error of the mean (N=14). Both cTBS and iTBS showed increased TOJ threshold at T2 compared to T0 and T1. Histogram depicts the main effect of TIME showing a significant increase in TOJ threshold at T2. **E)** TOJ means and standard error of the mean averaged over cTBS and iTBS for T0 and T2 as a function of trial number (N=14). Impairments occur as the participant reaches threshold, but not at suprathreshold ISIs. Asterisks indicate significant post-hoc Tukey's HSD. Double asterisks indicate a significant main effect without differences in Tukey's post-hoc HSD.

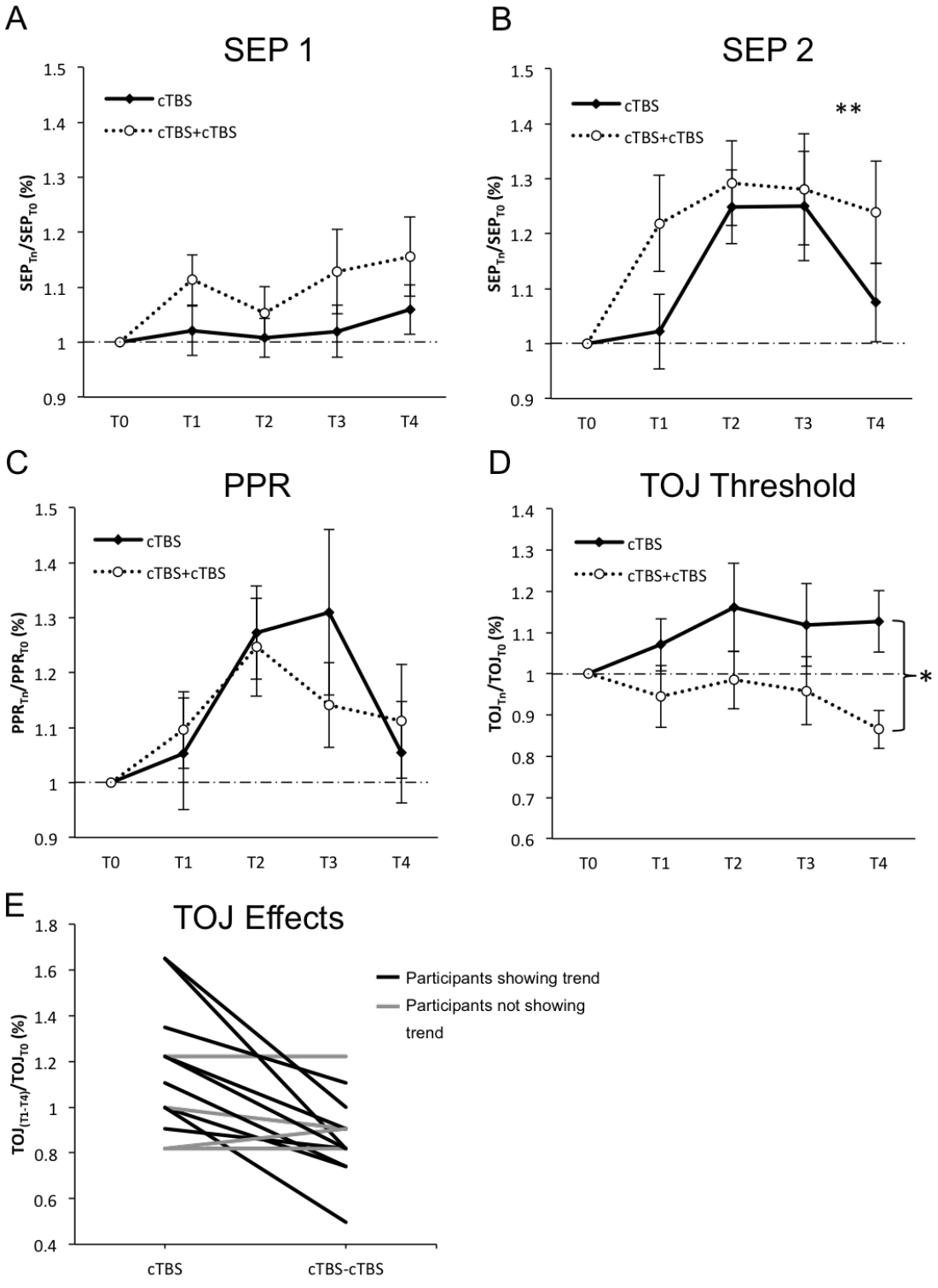

Figure 3.3: Metaplastic Effects of cTBS

Figure 3.3: Metaplastic Effects of cTBS. All data was normalized at each post time block to the baseline measurement T0. **A)** Group-averaged SEP 1 means and standard error of the mean (N=15). Compared to cTBS, cTBS-cTBS did not show any metaplastic effects. **B)** Group-averaged SEP 2 means and standard error of the mean (N=14). A significant effect of TIME was revealed, however post-hoc Tukey's revealed no significant differences between time blocks. **C)** Group-averaged PPR means and standard error of the mean (N=14) where no significance was observed. **D)** Group-averaged TOJ means and standard error of the mean (N=14). Asterisks reveal significant effect of INTERVENTION ($p=0.018$) where cTBS is significantly different than cTBS. A trend towards improved TOJ performance is seen in cTBS-cTBS at T4. **E)** Data from individual participants for TOJ (average of T1 through T4) depicting trend for decreased thresholds after cTBS-cTBS versus cTBS. Asterisks indicate significant post-hoc Tukey's HSD. Double asterisks indicate a significant main effect without differences in Tukey's post-hoc HSD.

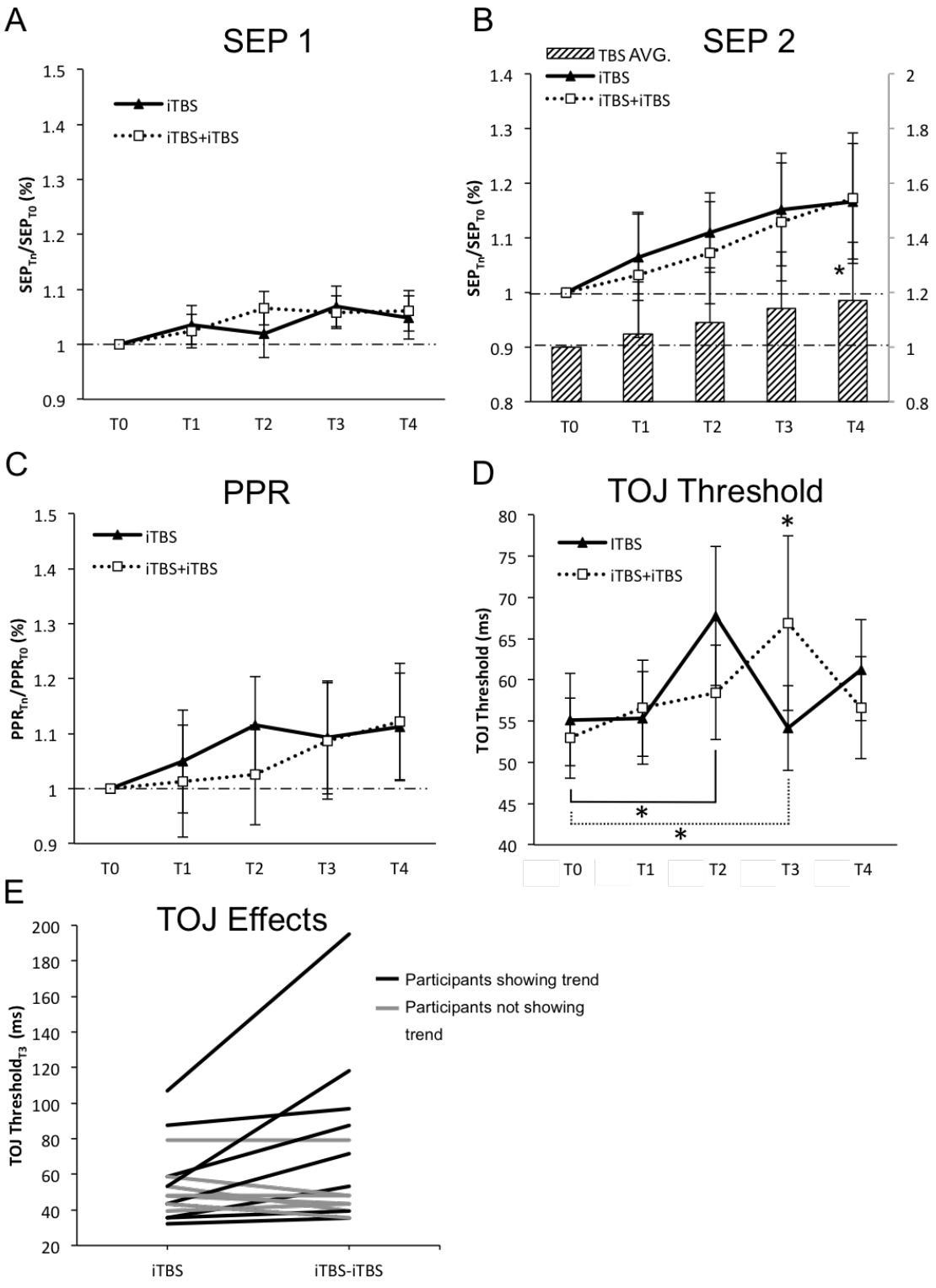

Figure 3.4: Metaplastic Effects of iTBS

Figure 3.4: Metaplastic Effects of iTBS. All data for SEP 1, SEP 2 and PPR was normalized to the baseline measurement T0 when T0s were statistically different. **A)** Group-averaged SEP 1 means and standard error of the mean (N=16) did not differ between interventions. **B)** Group-averaged SEP 2 means and standard error of the mean (N=15). ITBS did not differ from iTBS-iTBS. A significant effect of TIME revealed differences between T1 and T4 (main effect shown in histogram). **C)** Group-averaged PPR means and standard error of the mean (N=15). ITBS did not differ from iTBS-iTBS. **D)** Group-averaged TOJ means and standard error of the mean (N=16). A significant TIME x INTERVENTION interaction effect ($p=0.032$) revealed as increases in TOJ at T3 following iTBS-iTBS compared to iTBS. **E)** Data from individual participants for TOJ (at T3) depicting trend for increased thresholds after iTBS-iTBS versus iTBS.

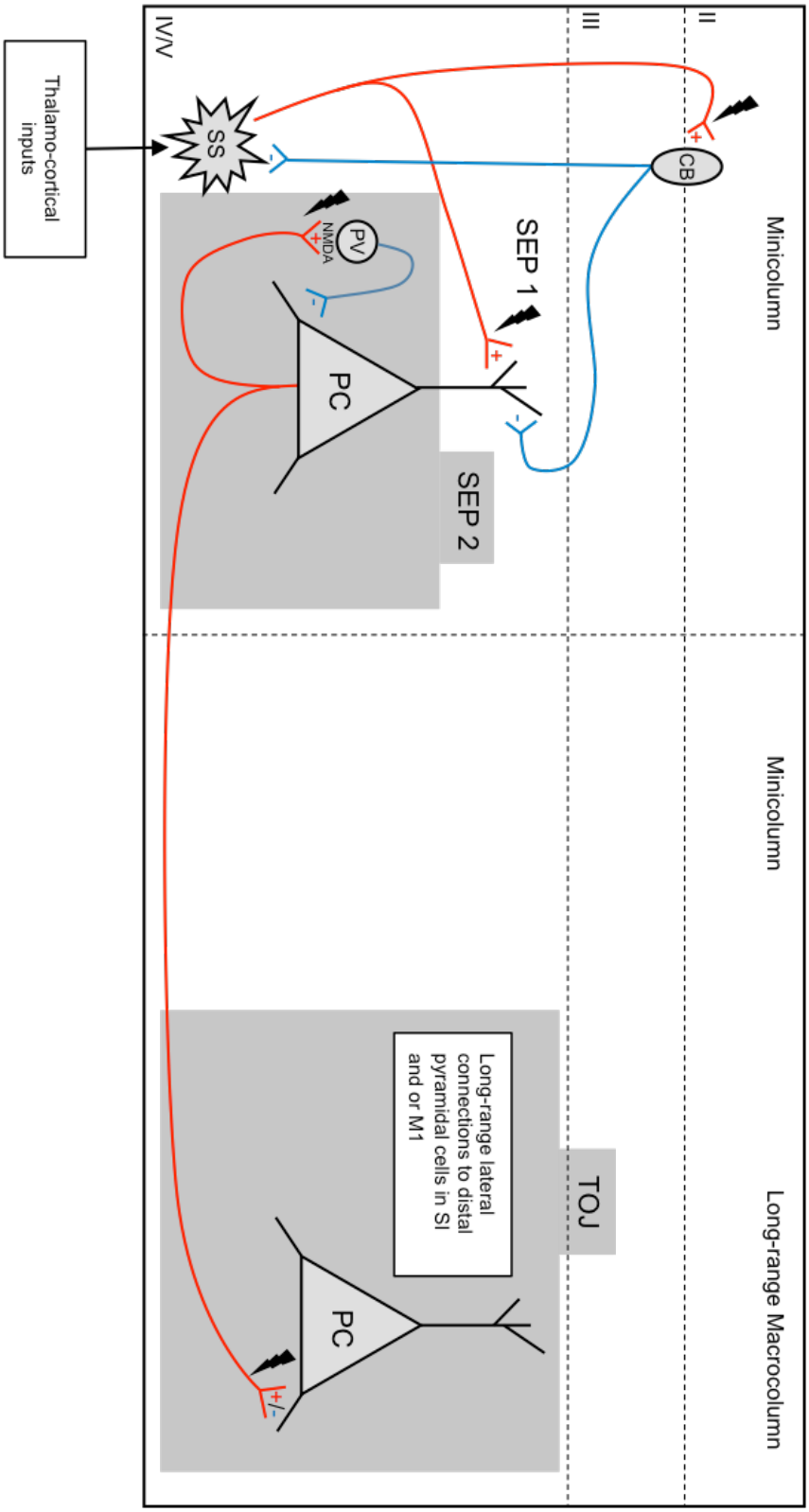

Figure 3.5: Model of Plastic and Metaplastic Effects in SI

Figure 3.5: Model of Plastic and Metaplastic Effects in SI

Baseline SI mechanisms: SEP 1: Sensory information is passed by spiny stellate cells (SS) to the apical dendrites of the pyramidal cell via excitatory inputs. The output of the pyramidal cell synapses on the basal dendrites of neighboring macrocolumn pyramidal cells. The summation of pyramidal cell activation leads to the generation of the SEP 1. **SEP 2:** In addition to synapsing on the pyramidal cell, SS cells also synapse on CB-expressing inhibitory interneurons that live within layers II/III of SI[118]. Evidence from animal literature suggests these CB cells act to inhibit the pyramidal cells within the microcolumn through synapses on superficial dendrites[119]. Additionally, the output from the pyramidal cells synapse on PV-expressing inhibitory interneurons, via NMDA receptors, living within layers IV/V of SI. These PV cells synapse perisomatically onto the pyramidal cell itself, while also synapsing with basal dendrites of pyramidal cells in neighboring macrocolumns. The inhibition provided by the CB-expressing cells, perisomatic PV-expressing cells and lateral PV-expressing cells results in overall inhibition of the pyramidal cells and thus reduced SEP 2 compared to SEP 1.

TOJ: Clear distinctions between receptive fields are responsible for tactile acuity, however the precise cortical mechanisms are unknown. The ability to make this distinction relies on GABAergic inhibition acting via inhibitory projections that can operate between cortical columns. This inhibition, when given adequate time to return to baseline, aids in the correct localization of a tactile stimulus. However, when stimuli are delivered in short succession (ie. when the ISI shortens) this inhibition cannot return to baseline and we can no longer accurately determine the order of stimuli.

Effects of TBS and Metaplasticity: TBS protocols delivered to SI are thought to generate LTD on PV and CB neurons, thereby reducing the activity in inhibitory interneurons and leading to an overall disinhibition within SI cortex[71]. I propose that in humans the TBS-induced increase in SEP 2 is primarily mediated by a reduction in recurrent inhibition due to LTD induced at NMDA synapses located on PV inhibitory interneurons. These interneurons receive their input from recurrent collaterals of pyramidal cells, forming a synapse that is glutamatergic and is blocked by NMDA antagonist[96]. This would support the requirement for NMDA receptors in TBS-induced effects, which when blocked abolish the effects of cTBS and iTBS[120]. Further, this model may provide an explanation for the increase in magnetic resonance spectroscopy detected GABA in human sensorimot[121]or cortex that follows cTBS such that GABA concentration may increase in presynaptic stores following hypoactivity within PV and CB neurons. Long range lateral projections to distal pyramidal cells in SI and or M1 can be EPSP dominant at low stimuli and IPSP dominant at high stimuli. Therefore either LTD at the inhibitory synapse or LTP at the excitatory synapse would create increased excitation that would result in reduced TOJ. Both cTBS-cTBS and iTBS-iTBS result in a reversal of TOJ impairments seen following cTBS or iTBS with no changes to SEP 2, therefore it is likely that metaplasticity operates via long-range lateral connections but not at those within the minicolumn.

Table 3.1: Statistical outcomes of two-way ANOVAs on data within each intervention for each dependent measure.

	Dependent Measure			
Two-way ANOVA	**SEP 1**	**SEP 2**	**PPR**	**TOJ Threshold**
All 6 Interventions	TIME $_{(3,45)}$ = 7.25 *p = 0.0005** *T1<T4* *T2<T4* INTERVEN $_{(5,74)}$ = 0.79 *p* = 0.5577 TIME x INTERVEN $_{(15,220)}$ = 0.53 *p* = 0.9213	TIME $_{(3,45)}$ = 2.80 *p* = 0.0508** INTERVEN $_{(5,70)}$ = 0.82 *p* = 0.5405 TIME x INTERVEN $_{(15,210)}$ = 0.89 *p* = 0.5725	TIME $_{(3,45)}$ = 2.44 *p* = 0.0767 INTERVEN $_{(5,70)}$ = 0.56 *p* = 0.7315 TIME x INTERVEN $_{(15,210)}$ = 1.13 *p* = 0.3267	TIME $_{(3,45)}$ = 1.45 *p* = 0.2413 INTERVEN $_{(5,73)}$ = 1.36 *p* = 0.2476 TIME x INTERVEN $_{(15,219)}$ = 1.32 *p* = 0.1926
cTBS vs. iTBS	TIME $_{(3,45)}$ = 0.99 *p* = 0.4072 INTERVEN $_{(1,15)}$ = 0.04 *p* = 0.8503 TIME x INTERVEN $_{(3,43)}$ = 0.56 *p* = 0.6457	TIME $_{(3,42)}$ = 3.183 *p = 0.0335** T1<T3 INTERVEN $_{(1,14)}$ = 0.056 *p = 0.817* TIME x INTERVEN $_{(3,42)}$ = 2.625 *p = 0.063*	TIME $_{(3,42)}$ = 2.759 *p = 0.054*** INTERVEN $_{(1,14)}$ = 0.297 *p = 0.594* TIME x INTERVEN $_{(3,42)}$ = 1.827 *p = 0.157*	TIME $_{(4,52)}$ = 3.424 *p = 0.015** *T0<T2* *T1<T2* INTERVEN $_{(1,13)}$ = 0.133 *p = 0.722* TIME x INTERVEN $_{(4,52)}$ = 0.343 *p =0.847*
cTBS vs. cTBS−cTBS	TIME $_{(3,42)}$ = 1.648 *p = 0.193* INTERVEN $_{(1,14)}$ = 1.829 *p = 0.198* TIME x INTERVEN $_{(3,45)}$ = 0.647 *p = 0.589*	TIME $_{(3,39)}$ = 2.87 *p = 0.048*** INTERVEN $_{(1,13)}$ = 1.22 *p* = 0.2889 TIME x INTERVEN $_{(3,39)}$ = 0.74 *p* = 0.5334	TIME $_{(3,39)}$ = 3.008 *p = 0.066* INTERVEN $_{(1,13)}$ = 0.067 *p = 0.800* TIME x INTERVEN $_{(3,39)}$ = 1.038 *p = 0.387*	TIME $_{(3,39)}$ = 0.943 *p = 0.429* INTERVEN $_{(1,13)}$ = 7.270 *p = 0.0183** TIME x INTERVEN $_{(3,39)}$ = 0.845 *p = 0.478*
iTBS vs. iTBS−iTBS	TIME $_{(3,45)}$ = 1.27 *p* = 0.2963 INTERVEN $_{(1,15)}$ = 0.04 *p* = 0.8470 TIME x INTERVEN $_{(3,45)}$ = 0.86 *p* = 0.4688	TIME $_{(3,42)}$ = 3.067 *p = 0.0381** *T1<T4* INTERVEN $_{(1,14)}$ = 0.049 *p = 0.828* TIME x INTERVEN $_{(3,42)}$ = 0.096 *p = 0.962*	TIME $_{(3,42)}$ = 1.072 *p = 0.371* INTERVEN $_{(1,14)}$ = 0.081 *p = 0.781* TIME x INTERVEN $_{(3,42)}$ = 0.431 *p = 0.732*	TIME $_{(4,60)}$ = 2.313 *p = 0.106* INTERVEN $_{(1,15)}$ = 0.038 *p = 0.849* INTERVEN x TIME $_{(4,60)}$ = 2.842 *p = 0.0317** iTBS: T0<T2 II: T0<T3 I vs II: iTBS T3 < IIT3

* indicates significance at $p \leq 0.05$. ** indicates a significant main effect with an insignificant post-hoc Tukey's HSD

Table 3.2: Means in millivolts (SEP 1 and SEP 2) and milliseconds (TOJ) and standard error of the mean for each intervention, dependent measure and time block.

	T0 (baseline)	T1 (5 minutes)	T2 (25 minutes)	T3 (50 minutes)	T4 (90 minutes)
cTBS					
SEP 1	3.85±0.508	3.98±0.535	4.03±0.592	3.74±0.536	3.86±0.511
SEP 2	1.42±0.170	1.44±0.203	1.72±0.208	1.66±0.194	1.50±0.196
PPR	0.431±0.047	0.4217±0.041	0.530±0.063	0.503±0.053	0.433±0.048
TOJ	48.761±3.834	50.9013±4.103	55.835±6.566	52.447±4.373	54.857±5.918
iTBS					
SEP 1	3.91±0.473	3.96±0.454	3.93±0.473	4.14±0.497	4.05±0.474
SEP 2	1.45±0.161	1.50±0.186	1.58±0.180	1.59±0.200	1.62±0.211
PPR	0.458±0.063	0.4344±0.047	0.472±0.054	0.452±0.053	0.467±0.054
TOJ	55.169±5.567	55.3707±5.633	67.734±8.405	54.165±5.161	61.178±6.112
cTBS-cTBS					
SEP 1	3.85±0.505	4.06±0.444	3.94±0.514	4.08±0.487	4.17±0.475
SEP 2	1.31±0.180	1.49±0.169	1.58±0.175	1.60±0.212	1.55±0.183
PPR	0.394±0.049	0.4143±0.046	0.466±0.047	0.438±0.058	0.405±0.051
TOJ	58.373±4.677	54.4131±5.414	58.509±6.196	56.516±6.036	52.884±5.600
iTBS-iTBS					
SEP 1	4.21±0.482	4.25±0.494	4.47±0.550	4.48±0.560	4.51±0.589
SEP 2	1.56±0.186	1.59±0.236	1.67±0.236	1.72±0.239	1.81±0.261
PPR	0.413±0.039	0.4169±0.058	0.425±0.060	0.428±0.049	0.446±0.053
TOJ	52.947±4.868	56.5651±5.850	58.452±5.709	66.890±10.611	56.651±6.197
cTBS-iTBS					
SEP 1	3.78±0.537	3.93±0.626	4.04±0.622	4.02±0.580	4.02±0.574
SEP 2	1.59±0.195	1.78±0.286	1.90±0.281	1.88±0.289	2.01±0.323
PPR	0.483±0.050	0.4953±0.050	0.5323±0.059	0.501±0.049	0.509±0.058
TOJ	54.834±3.545	54.9465±4.396	61.750±6.214	59.191±5.717	55.594±5.743
iTBS-cTBS					
SEP 1	3.91±0.505	4.09±0.532	4.29±0.602	4.27±0.602	0.04.52±0.616
SEP 2	1.78±0.226	1.88±0.294	1.84±0.263	1.95±0.273	1.94±0.240
PPR	0.491±0.050	0.4743±0.051	0.453±0.050	0.538±0.073	0.468±0.045
TOJ	52.184±3.460	61.7957±7.405	54.357±5.754	57.714±6.626	55.063±5.296

Chapter 4: General Discussion

4.1 Introduction

The focus of this Master's thesis was to investigate how metaplasticity operates within SI and to expose differences in SI physiology and tactile perception following the application of plasticity and metaplasticity TBS protocols. The experiment consisted of two plastic and four metaplastic TBS protocols during which TBS was delivered either singly or in succession, respectively. The aim of the study was three-fold: a) to evaluate differences between the two plastic protocols: cTBS and iTBS delivered at 30 Hz over SI, b) to examine if and how the addition of a second, homogeneous protocol would alter the effects of a single, plastic protocol, and c) to learn whether a metaplasticity protocol, when delivered over SI would create longer lasting changes to physiological and tactile perceptual measures compared to a plasticity protocol. This is the first study to examine how metaplasticity operates within SI and the first to investigate TBS-induced effects on physiology and tactile perception concurrently. The results of this study show that of the 6 protocols delivered, only TBS followed by its homogeneous TBS produces metaplasticity as measured by changes in TOJ. Metaplasticity was most prominent following cTBS-cTBS where impairments in TOJ subsequent to a single cTBS protocol were abolished and TOJ performance demonstrated a trend towards improvements persisting at least 90 minutes following stimulation. ITBS-iTBS also resulted in metaplastic effects. However this effect was confined to a single time block at 50 minutes post stimulation. No metaplastic effects were present in any of the measures of SI physiology suggesting that 1) the neural mechanisms by which TBS metaplasticity operates is distinct between SEPs and TOJ, and/or 2) SEPs are less sensitive to these

metaplasticity changes, and/or 3) SEPs cannot resolve any subtle changes associated with metaplasticity. Last, it was observed that cTBS and iTBS act similarly in their effects on TOJ and SEPs suggesting that a) the mechanism by which TBS operates in SI is distinct from that by which it operates in M1 and b) that the parameters of stimulation may create observable differences in excitability and tactile perception. The below discussion addresses the impact of the thesis research, as well as the advantages and limitations of the techniques used.

4.2 Impact of Thesis Research

The research conducted in this thesis has provided a novel contribution to the field of sensorimotor neuroscience. While research to date has focused on metaplasticity within M1, this is the first study to investigate TBS-induced effects of metaplasticity within SI. SI has been repeatedly shown to be a promising target for inducing plasticity, with the ability to create changes in tactile perception and to influence motor output via direct cortical connections with M1[4,7,9,11,12]. Animal studies suggest that direct disruption of SI neurons produces decrements in motor performance and an increase in the resting level of activity of M1 neurons [122,123]. Research in humans demonstrates that cTBS applied to SI can facilitate motor cortical excitability, thus providing evidence for an alternate approach to changing motor function[7,9]. Plastic changes are most often demonstrated in terms of changes in excitability or intracortical circuitry; the present study adds to the literature by introducing the behavioural measure of tactile perception. SI physiology measured with SEPs is shown in this study to be highly resistant to the metaplastic changes induced by TBS. There is a distinction between physiological and direct tactile

perceptual measures, where metaplasticity can be observed with TOJ but is not evident with SEP 1, SEP 2 or PPR. Future studies of SI may consider a single or battery of tactile perceptual measures in addition to, or in place of, evoked potentials measured via EEG.

Of highest importance is the impact of this research to clinical populations, where non-invasive plasticity-inducting TMS techniques are under consideration as potential therapeutic avenues. TMS-induced plasticity stimulates neural changes lasting up to approximately one hour in length and creates a window in which individuals with motor deficits may have a heightened ability to produce movements. Select studies have investigated paired associative TMS[124] or TBS[125] protocols that, when delivered prior to a period of motor training are intended to capitalize on the cortical enhancements during this time; in both cases, performance on their respective motor task is improved. Motor deficits are generally considered to be of utmost importance for rehabilitation, however sensory deficits can greatly alter an individual's ability to perform movement as evidenced by real[126] and virtual[75] lesion studies. Indeed, targeting SI with peripheral stimulation[127] or cTBS[128] can improve movement initiation and motor learning post-stroke if motor practice follows. The results from this thesis can be used to inform future studies aiming to improve tactile perception and/or motor output in clinical populations such as stroke and focal hand dystonia, where deficits in SI are likely to influence tactile processing as well as motor performance.

4.3 Advantages to Metaplasticity

Plasticity is dependent upon the immediate state of the postsynaptic neuron and is directly influenced by recent activity within the cell. Metaplastic effects are produced

when this recent activity acts to prime future changes and works to prevent the cell from entering a state of excessive LTP or LTD, a term referred to as Homeostatic metaplasticity. This study attempts to use metaplasticity to its advantage, by controlling the state of the postsynaptic cell by applying an initial TBS protocol and delivering a subsequent protocol to enhance the effects of the first. Theoretically, if the cell is in a state of LTD, it has a strong future propensity for LTP and thus the delivery of a LTP-inducing TBS protocol, may be capable of extending the degree and/or time course of LTP effects that is normally observed following a single TBS protocol. The results from this thesis suggest that TBS delivered in succession can create metaplastic effects that reverse the effects (cTBS-cTBS) or have an extended time course (iTBS-iTBS) compared to the effects of the respective plastic protocol. Further, delivering two protocols that individually create LTD-like effects in tactile perception results in not only the reversal but a tendency towards LTP-like effects. This is the first study to see improvements in touch perception following metaplastic TBS over SI and the first to identify perceptual changes lasting for a period of 90 minutes; collectively these results suggest that metaplasticity is a promising avenue for eliciting such changes.

4.4 Limitations of Techniques

One important limitation in the research is the use of SEPs to assess changes in SI physiology. SEPs are an artificially evoked measure of activity within SI and as such do not represent a naturally occurring measure of cortical excitation. Consequently, SEP 1, 2 and PPR may not truly reflect the degree and accuracy of tactile perception. Indeed, methodological studies suggest that the SEP component evolves over time as a direct

result of repeated median nerve stimulation although this effect is pronounced at high stimulation frequencies[41]. Further, the TMS parameters selected for the two TBS protocols likely contributed to the atypical effects seen following cTBS. Though cTBS delivered at 30 Hz has previously been shown to be a more consistent protocol to induce excitability changes in M1[8], this modified protocol is relatively untested in SI with the exception of one known study[68]. The lower frequency of pulse delivery may have contributed to the similarities in cTBS and iTBS protocols. Other parameters such as the intensity of TBS stimulation have been shown to play a key role in the magnitude and timing of plastic and metaplastic changes[87] although consistent effects have been demonstrated within a limited intensity range[8]. Further methodology research is required to fully understand how TBS frequency plays a role in excitation of SI. A final limitation of the current study is that the population selected for recruitment was young, healthy individuals. While this research lends itself well to the development of a TMS-based therapeutic protocol, the population studied does not match the typical age range of a clinical population such as stroke where the greatest prevalence is in adults aged ~65 or older[129]. As such, the results may not be generalizable to older populations. A future avenue for research would be to investigate TBS-induced metaplasticity in an aging population.

4.5 Concluding Statements

The research presented in this thesis provides evidence for metaplasticity in SI following TBS. Specifically, tactile perception is sensitive to metaplastic effects, where cTBS-

cTBS elicits a reversal of the TOJ deficits seen following a single cTBS. iTBS-iTBS also demonstrates metaplastic effects, but is limited to a shorter time course of effects, lasting approximately 50 minutes post TBS. Additionally, cTBS and iTBS are shown to produce similar changes in SEPs and PPR as well as in TOJ when delivered over SI. This research suggests a role of long-range lateral inhibitory projections as a mechanism by which TBS-induced metaplasticity operates in SI. Most importantly, this research provides a novel approach for changing tactile perception and future research should consider testing the applicability of metaplastic TBS in aging and clinical populations with sensory tactile deficits. Furthermore, this research raises questions regarding the standardization of TBS parameters and physiological measures, specific to SI to more accurately depict the sensory changes occurring. With this knowledge, future research can aim to develop a metaplastic TBS protocol that when paired with motor rehabilitation, can be used in a rehabilitation setting as a therapeutic technique aimed at recovering sensory and potentially motor function.

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