INFLUENCE OF SI ON INTERHEMISPHERIC INHIBITION

INFLUENCE OF PRIMARY SOMATOSENSORY CORTEX ON INTERHEMISPHERIC INHIBITION

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ABSTRACT

The control of unimanual and bimanual tasks is a highly orchestrated process in which primary motor cortex (M1) and primary somatosensory cortex (SI) play key roles. While somatic cortices are known to aid in the control of hand movements, the neural mechanisms by which they act remain largely unknown. One mechanism which is thought to mediate the control of hand movements between bilateral M1s is called interhemispheric inhibition (IHI), a neurophysiological mechanism by which one M1 is able to inhibit the contralateral M1, reducing the occurrence of unwanted movements, or enabling the performance of two differing tasks. Previous research suggests that IHI may be one mechanism by which SI aids in the control of hand movements and this thesis further examined this relationship. Two experiments were performed to investigate the influence of SI on IHI. Experiment 1 investigated the effects of direct modulation of SI cortical excitability on IHI. Experiment 2 investigated the effects of peripheral somatosensory inputs on IHI. The collective results of Experiments 1 and 2 suggest that SI can indeed modulate IHI from either the cortical or peripheral level, with increases in IHI seen following either intervention. Further, it was found that SI selectively modulates only the short latency phase of IHI (SIHI) as well as that mixed afferent inputs were most effective in altering SIHI. The novel findings of this thesis suggest that SI is indeed capable of aiding in the control of motor outputs and thus may be a possible target in future rehabilitative strategies.

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DECLARATION OF ACADEMIC ACHIEVEMENT

The entirety of this thesis has been written, and all experiments were conceived and performed, by myself. Conception of studies was aided by Dr. Aimee J. Nelson, and collection of data was aided by my fellow labmates, Mike Asmussen, Mark Jacobs, Kevin Lee, and Phil Tsang. In no way is any part of this thesis not my own work, and where necessary (Experiment 1) proper permissions from scientific journal publishers have been acquired to allow for reproduction of published material in this thesis. Further, for Experiment 1, my fellow labmates and supervisor have been credited with authorship status due to their aid in editing of the manuscript as well as with data collection.

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LIST OF ABBREVIATIONS

AMT	Active Motor Threshold
ANOVA	Analysis of Variance
CS	Conditioning Stimulus
CTBS	Continuous Theta Burst Stimulation
D2	Dopamine Receptor Subtype 2
DLPFC	Dorsolateral Prefrontal Cortex
EMG	Electromyography
FDI	First Dorsal Interosseous
GABA	Gamma (γ) Amino Butyric Acid
IHI	Interhemispheric Inhibition
I-Waves	Indirect Waves
LAI	Long Latency Afferent Inhibition
LIHI	Long Latency Interhemispheric Inhibition
LTD	Long Term Depression
LTP	Long Term Potentiation
M1	Primary Motor Cortex
MEP	Motor Evoked Potential
ms	Milliseconds
mV	Millivolts
MVC	Maximum Voluntary Contraction
NMDA	*N*-methyl-d-aspartate
NS	Nerve Stimulation
PMd	Dorsal Premotor Cortex
RMT	Resting Motor Threshold
RTMS	Repetitive Transcranial Magnetic Stimulation
SAI	Short Latency Afferent Inhibition
SI	Primary Somatosensory Cortex
SIHI	Short Latency Interhemispheric Inhibition
ST	Sensory Perceptual Threshold
TMS	Transcranial Magnetic Stimulation
TS	Test Stimulus
µV	Microvolts

Chapter 1: Goals of Thesis

Influence of primary somatosensory cortex on interhemispheric inhibition

1.0 Overview of Thesis

In humans and monkeys, contralateral homologous muscle representations are connected via transcallosal connections located in the posterior or anterior bodies of the corpus callosum, respectively (Human: [1,2]; Monkey: [3]. These connections have been functionally shown to mediate interhemispheric exchanges in electrophysiological studies in monkeys [4,5] and cats [6] and in transcranial magnetic stimulation studies in humans [7]. In cats [6], and humans [7] these connections have been shown to predominantly express inhibitory effects on contralateral homologous motor representations, an effect coined interhemispheric inhibition (IHI). IHI may be tested via a paired-pulse TMS paradigm in which a conditioning stimulus (CS) is applied to one hemisphere immediately preceding a second test stimulus (TS) applied to the homologous muscle representation of the opposite hemisphere at short latencies ranging from 6 to 50 ms [6-8]. In IHI it is thought that the CS activates transcallosal excitatory projections which synapse on populations of inhibitory interneurons in the contralateral TS hemisphere resulting in suppressed corticospinal motor output from the test hemisphere [7,9-11].

IHI may be one mechanism by which the control of unilateral and bimanual movements is modulated [12,13]. During the performance of unimanual tasks, IHI from the active hemisphere to the non-active hemisphere may be increased, a mechanism which is thought to prevent unwanted or mirrored movements in the non-active hand [12,14,15].

Alternatively, IHI may also be decreased from the active to non-active hemisphere, which is thought to allow for the rapid engagement of the non-active hand if the task requires it [13]

The ability to modulate IHI is not exclusive to homologous motor representations within primary motor cortex [16-18]. IHI tested with the CS located over non-homologous motor representations, such as the face, results in similar levels of inhibition as is seen when the CS is located over the homologous hand representation [16]. When the CS is located over the dorsal premotor cortex (PMd), both the short (SIHI) and long (LIHI) latency phases of IHI are present [16]. However, when the CS is located over non-motor areas such as SI or dorsolateral prefrontal cortex (DLPFC) inhibition of the TS pulse is observed at LIHI latencies only for both primary somatosensory cortex (SI) and dorsolateral prefrontal cortex (DLPFC) [16]. These findings are of significance because they suggest that IHI is able to be mediated by a disperse network of multiple motor and non-motor cortical areas which are able to inhibit the contralateral cortex via transcallosal projections.

This thesis is specifically focused on investigating the influence of SI on IHI. One reasoning for this is that SI possesses direct projections to M1 [19-22] positioning it to readily alter motor excitability and motor output of the hand, and therefore providing the opportunity for SI to modify motor control of the hands. Further, SI is commonly involved in neurogenic diseases and deficiencies in which altered hand control is seen, such as dystonia [23], Parkinson`s disease [24], stroke [25], and schizophrenia [26]. The ability to modulate SI activity to produce changes in motor outputs could potentially lead

to therapeutic and rehabilitative strategies to aid in the treatment of disorders such as these.

The overall goal of this thesis is to investigate the influence of SI on IHI. Two experiments were conducted with the first being conducted at the University of Waterloo, and the second at McMaster University.

1.1 Goals of Thesis

1.1.1 *Experiment 1 – Effects of cTBS applied over SI on bidirectional IHI*

To accomplish this goal of investigating the effects of SI on IHI, a plasticity-inducing repetitive transcranial magnetic stimulation (rTMS) protocol called continuous theta burst stimulation was applied over left SI and IHI was investigated bi-directionally (i.e. IHI recorded from left-to-right M1 (i.e. left hand) and from right-to-left M1 (i.e. right hand)). The significance of this study is that it provides novel information into how SI may modulate IHI bi-directionally as well as providing evidence that IHI is able to be modulated via changes in SI excitability.

1.1.2 Experiment 2 – Effects of somatosensory inputs on SIHI

To accomplish this goal of investigating the effects of SI on IHI, somatosensory inputs of differing contents, namely mixed afferent input from the median nerve and cutaneous

afferent input from the digital nerve, as well as different intensities were applied to either the left or right hand immediately preceding measurement of left-to-right (i.e. left hand) SIHI. The significance of this study is that it provides novel information to the ability of somatosensory inputs to modulate SIHI as well as, specifically, which contents and intensities of inputs are most readily able to induce changes in SIHI.

In the next section a review of relevant background literature will be presented. This section will begin with a review and discussion of TMS methodology and neural circuitry tested by TMS in these experiments, followed by a short review of the processing of somatosensory inputs at the cortical and peripheral levels.

Chapter 2: Review of Background Literature

2.1 Transcranial magnetic stimulation (TMS)

Transcranial magnetic stimulation (TMS) is a non-invasive method of brain stimulation, based upon Faraday's law of induction, which is used to investigate neural connectivity and function by depolarizing targeted populations of neurons via a rapidly changing magnetic field of variable intensity [27]. To create this magnetic field, a coil composed of wrapped conductive wiring is placed on the scalp over the location of interest and an electrical current is passed through the coil, resulting in a magnetic field induced perpendicular to the orientation of the coil which lasts for approximately 100 μs and is able to reach intensities of 2 Tesla or greater [28]. This magnetic field penetrates the scalp and is able to induce a subsequent secondary electrical current, opposite in direction to that in the coil, in the neurons located directly below the stimulating coil [28].

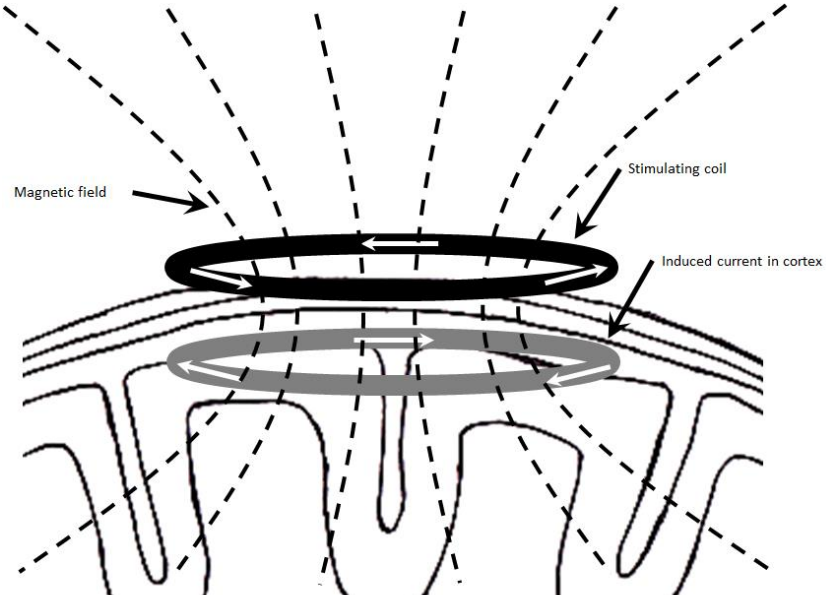

Figure 2.1. In TMS an electric current is induced in the brain via a rapidly changing magnetic field created by the stimulating coil. (adapted from Hallett, 2007)

Following a single-pulse of TMS, targeted neuronal populations may or may not depolarise, largely depending on the intensity of the secondarily induced current in the brain. However, the strength of this secondarily induced current in the brain is directly related to the current passing through the stimulating coil, and as such allows for application of sub-threshold or supra-threshold TMS pulses to the cortex [29].

2.1.1 Motor evoked potentials (MEPs)

A motor evoked potential (MEP) is the direct result of a TMS pulse applied over the motor cortex at a threshold or supra-threshold intensity and may be recorded from the contralateral muscle of interest [30]. Following a TMS pulse applied over a specific

muscle representation within MI with sufficient intensity to depolarise the neural tissue, an action potential is elicited and travels to the muscle of interest via the descending corticospinal tract [31]. At the muscle, this action potential results in the release of calcium and acetylcholine into the neuromuscular junction causing contraction of the muscle. This contraction can be recorded via electromyography (EMG) and is called an MEP. MEP peak-to-peak amplitude is most commonly used as a measure of corticospinal and spinal motoneuron activity [32,33], and as such changes in MEP amplitude are commonly used to gauge excitability of the corticospinal tract, with increases in MEP amplitude correlating to increased excitability and decreases in MEP amplitude representing decreased excitability. Other measures of MEPs, such as MEP duration, also provide valuable information concerning neural excitability and, as such, may be used in place of or in conjunction with MEP amplitude to fully gauge changes in neural excitability. Commonly, MEPs are recorded in muscles of the hand due to their relatively low threshold of depolarization and ease of location due to their large putative representations within M1.

2.1.2 Motor Thresholds

Motor thresholds may be measured via TMS by altering the intensity of the depolarising stimulus to determine the level of membrane excitability for a particular population of neurons during activity or at rest. This is useful from a clinical standpoint, as changes in motor thresholds have been reported in multiple patient groups [30]. Resting motor

threshold (RMT) is described as the lowest stimulation intensity required to evoke MEPs of minimum amplitude 50 μV in 5 of 10 consecutive trials [34]. Alternatively, active motor threshold is described as the lowest stimulation intensity required to evoke MEPs of minimum amplitude 100 or 200 μV in 5 of 10 consecutive trials while the targeted muscle is held at a slight contraction, usually 10-20% of the maximum voluntary contraction (MVC) [34]. While the above descriptions of RMT and AMT are the most commonly used, there is in fact no set definition of RMT or AMT, and as such methods vary widely across studies, making some measures difficult to understand and compare. However, in general these motor thresholds may be used to gauge changes in membrane excitability over time or as a means to calibrate intensity of TMS paradigms on an inter-subject basis. The ability to use motor thresholds to calibrate rTMS paradigm intensity on a subject by subject basis is extremely useful as threshold levels vary widely between individuals and applying these plasticity-inducing paradigms at a set level of each individuals motor threshold results in similar levels of stimulation across subjects regardless of inter-subject differences.

2.1.3 Repetitive transcranial magnetic stimulation (rTMS)

When applied in rapid succession, TMS is able to alter neural excitability for short periods of time, with effects mimicking those seen in long term depression (LTD) and long term potentiation (LTP) – like mechanisms [28,35]. The effects of rTMS are largely dependent on a number of factors, such as frequency of stimulation, duration of

stimulation, and intensity [36,37], with changes in frequency having the most marked effect. RTMS applied at low frequencies ($\leq$ 1 Hz) results in decreases in cortical excitability [38], while conversely, high frequency rTMS ($\geq$ 1 Hz) results in increases in cortical excitability [39].

Continuous theta burst stimulation (cTBS) is a patterned, low intensity rTMS paradigm consisting of bursts of three stimuli presented at a rate of 50 Hz with bursts being repeated every 200 ms [40].

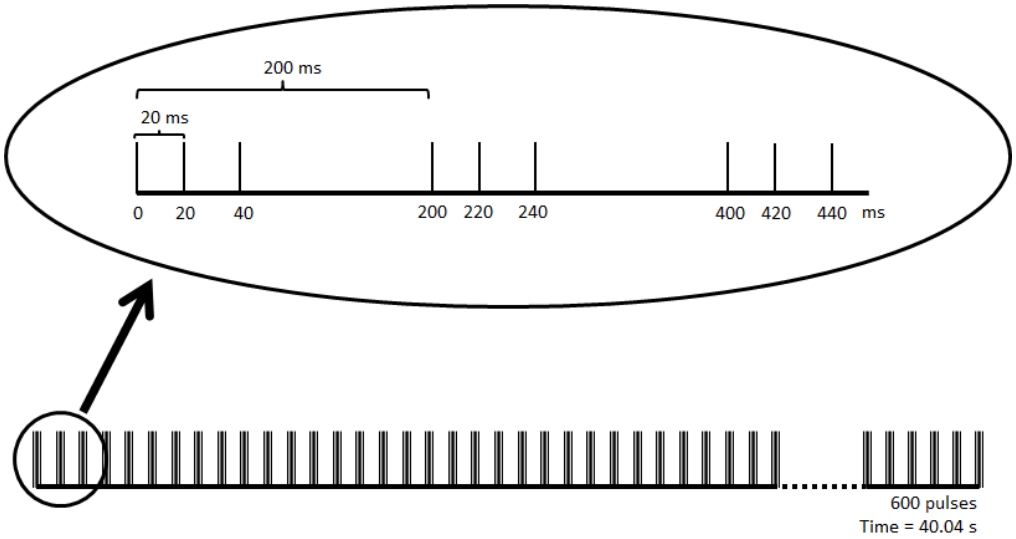

Figure 2.2. Continuous theta burst stimulation consists of three stimuli sent in bursts at a rate of 50 Hz repeated every 200 ms. (adapted from Cárdenas-Morales, 2010)

Designed to mimic protocols which induce LTP and LTD in animals [41,42], cTBS results in long lasting changes in cortical excitability. When applied over M1 long lasting decreases in cortical excitability are seen, with decreases lasting for up to one hour [40]. When applied over SI however, decreases in neural excitability are seen for much shorter

periods, with decreases in the amplitude of somatosensory evoked potentials being observed for up to 13 minutes following stimulation [43], high frequency oscillations 15 minutes following stimulation [44], and decreases in spatial and temporal tactile discrimination thresholds for up to 18 minutes following stimulation [45]. In humans, the mechanism by which these cTBS effects are modulated is still unknown; however magnetic resonance spectroscopy studies suggest increases in $GABA_A$ in the stimulated cortex following cTBS [46]. However, involvement of glutamatergic and dopaminergic systems is also suggested as cTBS effects are negated following blockage of NMDA receptors [47,48], and D2 receptors [49] respectively. Animal studies provide further insight into the mechanisms by which cTBS may act. Shortly following cTBS applied to rats, expression of proteins responsible for GABA synthesis [50,51] and presynaptic transport [52] are altered, with expression of the proteins responsible for GABA synthesis in the cytosol being decreased, and expression of the proteins responsible for presynaptic transport and GABA synthesis within the nerve terminals being increased [52]. These effects are reversed one day following application of cTBS, and may persist for up to a week post-stimulation [52].

2.1.4 Interhemispheric Inhibition (IHI)

Interhemispheric inhibition (IHI) is a neurophysiological mechanism by which bilateral M1s are able to inhibit each other. The ability of transcallosal projections to mediate motor output was originally shown in cats, with both inhibitory and excitatory projections

seen [6]. However, the area producing excitatory input was extremely small compared to the large inhibitory area surrounding the excitatory locus [6]. Further, at higher intensities the predominant effect was inhibition of the contralateral homologous motor representation, with the excitatory effects only present at much weaker stimulus intensities [6]. Peak inhibition was seen at latencies of 6-8 ms, minimally longer than the time needed for an impulse to traverse a direct pathway through the corpus callosum to the homologous muscle representation [6]. While it has been suggested that IHI may also be mediated via subcortical pathways [8], the argument for transcallosal routes seems more likely. Individuals who have corpus callosum lesions or abnormalities do not exhibit IHI [9,53,54], as well the strength of inhibition elicited by IHI paradigms is directly related to the number of fibres present and the integrity of those fibres in the corpus callosum [1,54]. Further, individuals who have experienced subcortical stroke exhibit normal IHI whereas patients who experienced cortical stroke [55,56] do not. Changes in IHI are exclusive to the cortex as changes in spinal reflexes are not seen during IHI [7].

IHI is readily tested via a paired-pulse TMS paradigm in which a conditioning stimulus (CS) is applied to one hemisphere immediately preceding a second test stimulus (TS) applied to the homologous muscle representation of the opposite hemisphere at a short latency of 6 to 50 ms [6-8].

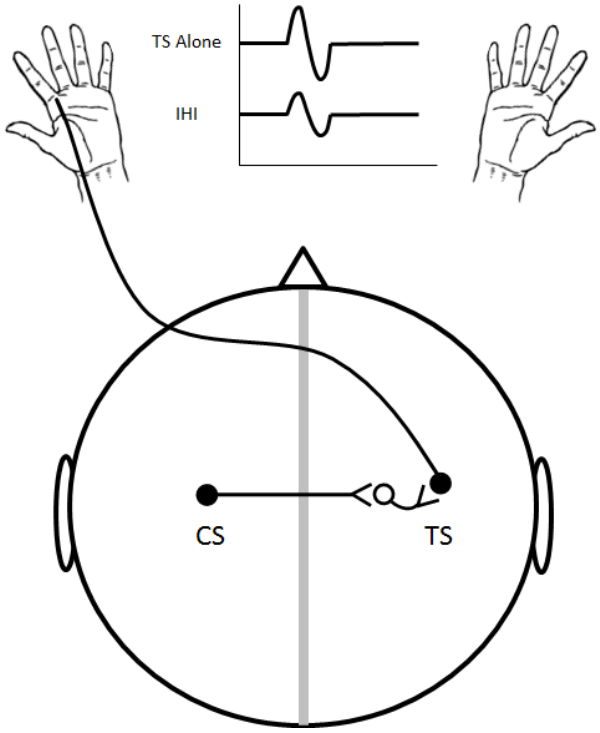

Figure 2.3. Interhemispheric inhibition consists of a conditioning stimulus applied to one hemisphere immediately preceding a second test stimulus to the opposite hemisphere which results in inhibition of motor output. Closed circles represent excitatory connections. Open circles represent inhibitory connections.

In IHI it is thought that the CS activates transcallosal excitatory projections which synapse on populations of inhibitory interneurons in the contralateral hemisphere resulting in suppressed corticospinal motor output in the test hemisphere [7,9-11] . The amount of inhibition induced by the CS pulse on the TS is largely dependent on the balance between the two stimuli. As the CS is increased for a set TS intensity, increased inhibition is seen [7,16,57], while the contrary is true for the TS, with an increasing TS intensity compared to a CS of set intensity resulting in decreased inhibition [7]. IHI exists

in two phases, a short interval inhibitory period (SIHI) seen when the latency between CS and TS is approximately 8-10 ms, and a long interval inhibitory period (LIHI) seen when the latency between CS and TS is approximately 40 ms [16,57]. SIHI and LIHI are governed by different mechanisms and may also serve different functions. LIHI is believed to be mediated by a $GABA_B$ mechanism [58-60] while the mechanism for SIHI is yet to be determined, though $GABA_A$ involvement seems likely via studies in rats [61] and cats [62].

IHI is modulated during movement and contraction. Contraction at 50 % MVC of the target muscle results in decreased SIHI, but has no effect on LIHI [57]. However, during performance of a unimanual pen holding task, both SIHI and LIHI are decreased bi-directionally, an effect further demonstrated during tonic contraction of either hand [13]. Differences in these findings may relate to the degree of contracture, with the former being at 50 % MVC and the latter two being performed at 20 % MVC [13,57]. Modulations in IHI are also seen immediately prior to movement of the dominant, but not non-dominant, hand, with a release of SIHI resulting in facilitation being observed [12], suggesting that a degree of hand-dominance effects may be present. However, this effect is controversial as some studies suggest differing effects of IHI from dominant to non-dominant hemisphere [63,64], while other studies show no evidence of dominance effects for IHI [13,65].

2.1.5 Effects of rTMS paradigms on IHI

When applied over M1, low-frequency rTMS reduces SIHI in the ipsilateral hand to stimulation [66,67] while LIHI is either reduced [66] or unchanged [67]. Differences in the effects of LIHI following rTMS are likely attributed to differing orientations of induced current in the brain with the initial phase of the TMS pulse inducing posterior-to-anterior current resulting in changes in both SIHI and LIHI, while rTMS applied with the initial phase of the induced current being in the anterior-to-posterior direction resulting in changes to SIHI alone [66]. At present, no study has investigated the effects of rTMS applied over SI.

Following cTBS applied over M1, IHI is unaltered [68]. Lack of effects of cTBS as compared to rTMS paradigms is likely attributable to the low intensity of the cTBS paradigm, with cTBS being applied at sub-threshold intensities [68] and rTMS paradigms which successfully altered IHI being applied at suprathreshold intensities [66,67].

IHI is also modulated following stimulation of Brodmann area 5, an area associated with the ability to perform complex hand movements involving opposable thumbs in primates and humans [69]. Following cTBS over area 5, SIHI is significantly reduced in the ipsilateral hand to stimulation while no changes are seen in either SIHI for the contralateral hand to stimulation or for LIHI bilaterally [70] .

2.2 Somatosensory inputs alter IHI

Following temporary occlusion of somatosensory inputs via ischaemic nerve block, IHI is decreased from the affected hemisphere to the unaffected hemisphere [71]. Further, muscle belly vibration results in increased IHI from the unaffected hemisphere to the affected hemisphere [72].

Presenting a peripheral somatosensory input, usually via electrical stimulation of the median nerve, prior to a TMS pulse at latencies of approximately 22 or 200 ms, results in a decrease in motor output, effects called short afferent inhibition [73] and long afferent inhibition [74], respectively. When a somatosensory input is applied at a short latency prior to the activation of the TS, such as in a normal SAI paradigm, SIHI is significantly reduced [75]. Alternatively, if a somatosensory input is presented at a longer latency prior to the activation of the TS, such as in a normal LAI paradigm, reductions in both SIHI and LIHI are seen [76].

While the effects of cTBS applied over SI on IHI have not been investigated previously, there is evidence to suggest that this may be so. Following cTBS applied over SI oxy-hemoglobin concentrations in the contralateral M1 and SI were reported [77], suggesting transcallosal changes in resting cortical activity. Changes in contralateral hemisphere resting cortical activity following cTBS applied over SI are further confirmed by changes in MEP amplitudes, however the direction of effects differs [77,78].

2.3 Primary somatosensory cortex

2.3.1 Anatomy and function

Primary somatosensory cortex (SI), located in the post-central gyrus, is composed of four cytoarchitecturally independent subdivisions labelled as Brodmann areas 1, 2, 3a and 3b in both monkeys and humans [79-81]. Within SI the contralateral side of the body, as well as the face, are represented in a logical, somatotopic order with the lower limb representation being most medial, starting with the foot, and progressing laterally to the arm, hand, and face as shown via functional magnetic resonance imaging [82] and positron emission tomography studies [83]. This logical progression is also held true for individual digits of the hand, with the 5^{th} finger being located most medial, followed by the 4^{th} through 2^{nd} digits and thumb [84]. These techniques have also shown that multiple overlapping representations of each area exist [80,83,85-88], with overlaps being least pronounced in area 3b in monkeys [79] and in areas 3a and 3b in humans [84]. These somatotopic representations are further expressed in terms of cortical area, with those areas with the highest density of peripheral receptors receiving greater cortical area than those with less numerous receptors, and as such, the hand representation within SI is much larger in comparison to other areas [89].

Functionally, SI may also be divided into 4 distinct areas, with each of areas 1, 2, 3a, and 3b exhibiting differences in processing of differing submodal inputs. Area 3a is composed predominantly of afferent inputs projecting from deep tissues such as muscles and joints (cat: [90]; monkey: [91,92] although contributions from muscle afferents has been

suggested [21], while area 3b is largely associated with processing of cutaneous inputs [92]. Further, areas 1 and 2 are associated with processing of cutaneous and deep afferent inputs respectively, albeit to lesser extents than areas 3b and 3a [92].

Functionally, each separate area of SI plays a different role. Following lesions to SI in monkeys, gross changes in somatosensation are seen, with lesions to area 1 resulting in impairment in texture and spatial discrimination tasks [93], area 2 inhibiting the ability to discriminate between shapes [93], and area 3b resulting in deficiency of all tasks requiring tactile feedback [94]. Removal of an entire representation, such as the arm or hand, also results in tactile discrimination impairment [95].

Bilateral SI is connected via transcallosal fibres with the density of connection varying largely between architectonic areas, with area 2 having moderately dense connections, area 1 having a minimal number of connections, and area 3b having relatively few [96]. Further the number of transcallosal connections varies between representation, with the face and trunk having more dense connections than the hand and foot, which have been reported to have fewer [96] or no connections [20] depending on the species of monkey investigated (owl monkey: [96]; rhesus monkey: [20]). Ipsilaterally, all areas of SI with the exception of area 3b possess direct projections to M1 [19-22].

2.3.2 Primary somatosensory cortex modifies primary motor cortex outputs

With the exception of area 3b, SI has direct projections to primary motor cortex [19-22] and as such is able to modify neural activity within M1, with changes in motor control and cortical excitability being observed. Following lesioning or injection of muscimol, a $GABA_A$ agonist, into the postcentral gyrus, impairments in motor learning [97], and fine motor coordination [94], respectively, are seen. Following cooling of the postcentral gyrus, impairments in gross motor control and coordination are observed, as well as an increase in baseline M1 activity [98]. Changes in M1 excitability may also be observed following tetanic stimulation of SI in cats [99,100]. Further, as mentioned previously, arrival of somatosensory input to SI results in decreases in motor output when the latency between sensory input and motor output is at either short (i.e. 20 ms) [73] or long (i.e. 200 ms) [74] latencies.

Chapter 3: Experiment 1

Continuous theta-burst stimulation over the primary somatosensory cortex modulates interhemispheric inhibition

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3.1 INTRODUCTION

Somatosensory and motor cortices play an important role in the control of hand movements. One mechanism that mediates hand movements is called interhemispheric inhibition (IHI). IHI exists between motor cortices in both hemispheres and is altered during hand movement. During one-handed movements, IHI may be increased to prevent unwanted movements of the opposite hand [1]. IHI may also be decreased to allow both hands to be engaged in the task if required [2]. Further, IHI is abnormal in neurophysiological disorders that affect hand movement such as stroke [3] and dystonia [4]. It is interesting to note that somatosensory abnormalities also exist in these

populations, suggesting that the somatosensory cortex may influence IHI in the control of hand movement.

In humans, the primary somatosensory cortex (SI) is able to modify neural activity within the primary motor cortex (M1) [5]. After continuous theta-burst stimulation (cTBS) over SI, neural activity within bilateral M1 is altered [6,7]. SI is similar to higher-order somatosensory area 5 in both cytoarchitecture and function [8], and, similar to findings from SI, cTBS over area 5 also alters the neural activity in bilateral M1 [9]. This is not surprising given that both area 5 and SI have direct projections with similar magnitudes of input to M1 [10], positioning both loci to alter motor excitability. Further, previous studies suggest that area 5 may also be involved in the integration of somatic inputs between hands [11]. Importantly, cTBS over area 5 has been shown to decrease IHI in the ipsilateral hand [12]. On the basis of their functional similarity, and the fact that both loci change M1 excitability bilaterally, it is possible that SI is also capable of altering the neural circuitry which underpins IHI.

In the present study we test whether SI is capable of altering IHI in support of SI's ability to influence the neural control of hand movement. The goal of this study was to determine whether SI is in fact able to modify IHI, similar to other somatosensory loci such as area 5 [12], as a possible mechanism to aid in the control of single and dual hand movements. To evoke IHI, one transcranial magnetic stimulation (TMS) pulse is applied over a motor representation in one M1 and a subsequent TMS pulse is applied over the homologous

motor representation in the opposite M1 [13,14] at a short (SIHI) or long (LIHI) latency. The first pulse is thought to activate excitatory transcallosal projections that synapse onto inhibitory interneurons in the contralateral hemisphere, resulting in suppressed corticospinal motor output evoked from the second pulse [13,15,16]. Given the functional and anatomical similarities between SI and higher-order somatosensory area 5, and the data supporting SI's influence on bilateral M1 [6,7] we hypothesized that cTBS over left-hemisphere SI would result in an increase in short latency IHI in the hand ipsilateral to cTBS. This finding would indicate that SI is indeed able to influence hand control by modifying transcallosal neural activity, further supporting the role of SI in the control of hand movement.

3.2 METHODS

3.2.1Participants

Sixteen individuals participated (11 men, mean age = 26.4, SD = 5.5). All participants were right handed as determined using a subset of the Edinburgh Handedness Inventory. Informed written consent was obtained from all participants prior to testing. This experiment followed the Declaration of Helsinki and was approved by the University of Waterloo.

3.2.2 Electromyography (EMG)

Muscle activity was recorded from the first dorsal interosseous (FDI) muscles of both the left and right hands using surface electrodes (9 mm Ag-AgCl) with the active electrode placed over the muscle belly and the reference electrode over the metacarpophalangeal joint. The electromyogram (EMG) was amplified x 1000 and filtered from 20-2500 Hz (Intronix Model 2024F; Intronix Technologies Corporation, Bolton, Canada). EMG was acquired using a Cambridge Electronic Device (Power 1401; Cambridge Electronic Design, Cambridge, UK) and analyzed offline using Signal software (Cambridge Electronic Design).

3.2.3 Interhemispheric Inhibition (IHI)

IHI was applied using two custom built 50 mm inner diameter figure-of-eight branding coils connected to two Magstim 200^2 stimulators (Magstim, Whitland, UK). Coils were positioned over the left and right M1 at an angle 45° to the midsagittal line. Motor hotspots, defined as the optimal location for eliciting motor-evoked potentials (MEPs) in the contralateral FDI, were located and marked using Brainsight Neuronavigation software (Rogue Research, Montreal, Canada) for M1 in each hemisphere using a standardised MRI. IHI consisted of delivering a test stimulus (TS) over the FDI motor hotspot in one hemisphere preceded by a conditioning stimulus (CS) over the contralateral homologous motor hotspot [13]. IHI was tested at two interstimulus intervals, 10 ms and 40 ms, reported previously as optimal interstimulus interval to test

SIHI and LIHI, respectively [17]. SIHI and LIHI were tested in both the left (left-to-right motor cortex) and right (right-to-left motor cortex) FDI. As the magnitude of IHI is dependent on the intensities of the test and conditioning pulses [13], the CS and TS intensities were set to elicit MEPs of ~1 mV in peak-to-peak amplitude and monitored throughout the experiment [2,12].

IHI was acquired before (T_0), and 5-20 min (T_1), 25-40 min (T_2), and 45-60 min (T_3) after cTBS in blocks of 40 trials such that each block randomly presented 10 repeats of the TS alone, CS alone, SIHI and LIHI. Two blocks were collected at each time point, one for IHI in the left and right FDI, respectively. For each participant, the order of IHI direction (i.e. left-to-right IHI, right-to-left IHI) was maintained across all time blocks, and the starting direction of IHI was counterbalanced across participants. Eight participants began with IHI recorded in the left hand, and eight in the right hand. A background EMG at rest was obtained during the pre-stimulus window of 3-25 ms in each trial before any TMS pulse to ensure that the participant was truly at rest during testing as even small levels of contraction have been shown previously to alter IHI [2].

3.2.4 Continuous theta-burst stimulation (cTBS)

CTBS was delivered using a MagPro stimulator (MCF-B65; Medtronic, Minneapolis, Minnesota) with a 90 mm outer diameter figure-of-eight coil in which the current flows in

a direction away from the handle in the initial phase of the biphasic pulse. CTBS was delivered over left-hemisphere SI using a 600 pulse protocol with the coil positioned 45° to the midsagittal line and the handle pointed in the posterior-lateral direction (i.e. induced current in the cortex in the anterior to posterior followed by posterior to anterior direction). The left-hemisphere SI target was digitally marked at a position 2 cm posterior to the FDI representation within M1 [18], measured using a standardized MRI in Brainsight Neuronavigation (Rogue Research). Active motor threshold (AMT) was determined at the left-hemisphere M1 hotspot using biphasic pulses in the anteroposterior-posteroanterior orientation with the cTBS coil and was defined as the lowest intensity required to evoke MEPs of at least 200 μV in five of 10 consecutive trials while holding a 10% maximal voluntary contraction of the right hand FDI muscle using visual feedback displayed on an oscilloscope of the rectified, integrated EMG signal. CTBS was delivered at 80% AMT.

3.2.5 Data Analysis

MEP peak-to-peak amplitudes for left and right FDIs were normalized to the unconditioned TS alone condition for each block. Normalized values of less than 1 represent inhibition and values greater than 1 reflect facilitation of corticospinal output. Only participants in whom the magnitude of IHI was equal to or less than 70% during the pre-cTBS block (T_0) were included in further analysis. This criterion was established to ensure that the magnitude of IHI in T_0 was within the range typically observed in healthy

adults [2,12,17] and to avoid excessive inhibition that would lead to a possible floor effect should inhibition increase after cTBS. Four one-way repeated measures analysis of variance (ANOVAs) were run on normalized MEP data (SIHI in the left FDI, SIHI in the right FDI, LIHI in the left FDI, and LIHI in the right FDI) using the within subject factor, TIME (four levels; T_0, T_1, T_2, T_3). ANOVAs were completed separately on SIHI and LIHI as performed previously [12,19] as each measure is thought to be mediated by different neural mechanisms [20,21]. Bonferroni-corrected *a priori* t-tests were used to test the hypothesis that SIHI in the left FDI would be increased at time points T_1 and T_3, in accordance with results from cTBS applied over somatosensory area 5 [12]. Statistical significance was set at a P-value of 0.05 or less.

3.3 RESULTS

All participants successfully completed the experiment. For SIHI right, SIHI left, LIHI right and LIHI left 14, 15, 15 and 14 people met the IHI criteria, respectively, and their data were included in further analysis. The group-averaged MEP amplitude for CS and TS alone are presented in Table 3.1. The average AMT at 200 μV was 29 ± 4.7 % maximum stimulator output (MSO). The average cTBS intensity applied was 23 ± 3.7 % MSO.

The group-averaged data for SIHI and LIHI (with standard errors) is shown in Figure 3.1. One-way repeated measures ANOVA revealed no effect of TIME for SIHI left ($F(3,42) = 1.98$, $p = 0.13$), SIHI right ($F(3,39) = 0.29$, $p = 0.83$), LIHI left ($F(3,39) = 2.18$, $p = 0.11$) or LIHI right ($F(3,42) = 0.18$, $p = 0.91$). To test the hypotheses of increased SIHI in left FDI at T_1 (5-20 min after cTBS) and T_3 (45-60 min after cTBS), Bonferroni-corrected paired t-tests were performed and revealed a significant increase in SIHI at T_3 (paired t-test, $p = 0.024$) similar to that observed after cTBS over left-hemisphere area 5 [12]. Background EMG analyzed using one-way repeated measures ANOVA revealed a significant effect of TIME on SIHI left ($F(3,42) = 2.81$, $p = 0.05$), but no effect of time on SIHI right ($F(3,39) = 1.35$, $p = 0.27$), LIHI left ($F(3,39) = 2.04$, $p = 0.12$), or LIHI right ($F(3,42) = 1.49$, $p = 0.23$) as shown in Figure 3.1. Post-hoc Tukey's test for SIHI left FDI revealed that the background EMG amplitude was not significantly different across time blocks.

3.4 DISCUSSION

In the present study we observed that SI influences IHI between M1 cortices. Specifically, short latency IHI was increased in the left hand after cTBS was applied over left-hemisphere SI. This result is similar to that reported for higher-order somatosensory area 5 [12] and supports the finding that SI influences neural activity in bilateral M1 [6,7]. These findings are significant as they reveal that SI alters the excitability of transcallosal connections that contribute to the control of single and dual-handed

movements. The neural mechanisms that may mediate such changes in the hand ipsilateral to cTBS are discussed below.

The ability of somatosensory cortices to modulate IHI holds particular importance for the control of single and dual handed movements. During the performance of a one-handed task, IHI is increased in the non-active hand, a response that is thought to inhibit unwanted or mirror movements in the resting hand [1]. Further, when a sensorimotor task is being performed, such as tool use, there is an even greater increase in IHI in the non-active hand [22], suggesting task-specific increases in IHI in the presence of somatosensory input. Our findings suggest that targeting the SI with cTBS may provide one opportunity to increase abnormally low levels of IHI, as seen in disorders such as dystonia [4,23] and potentially alter hand control in this population.

IHI is thought to be mediated through excitatory transcallosal projections between homologous M1 muscle representations that synapse on local populations of inhibitory interneurons that modulate corticospinal output [13,14]. The net result of this circuitry after a single TMS pulse is applied to one M1 is a concomitant suppression of corticospinal output in the contralateral M1 [13,15,16]. IHI may be divided into short and long latency components, each of which correspond to different sets of neuronal circuitry, with LIHI mediated through a $GABA_B$ mechanism [20] and SIHI suggested to be mediated through a $GABA_A$ mechanism [21]. Our findings suggest that SI does not alter

$GABA_B$ circuitry mediating LIHI but instead alters $GABA_A$ circuitry that may underpin SIHI.

In the present study, cTBS over left-hemisphere SI led to an increase in SIHI for 45 - 60 min after stimulation, a result similar to that after application of cTBS over higher-order somatosensory area 5 [12]. One suggestion is that cTBS delivered to either somatic locus increases the excitability of ipsilateral M1 excitatory transcallosal connections, which act to strongly excite inhibitory interneurons in the opposite M1 that, in turn, decrease the corticospinal output from that hemisphere. Further, cTBS delivered in the anterior-to-posterior direction over left-hemisphere SI or the left-hemisphere area 5 increases corticospinal output from left-hemisphere M1 [6,9]. Collectively, these data suggest that left-hemisphere somatosensory cortices influence both the transcallosal and corticospinal output of ipsilateral M1. It is interesting to note that changes in SIHI were seen exclusively in the hand ipsilateral to cTBS without altering SIHI in the opposite hand or LIHI bilaterally. Similarly, repetitive TMS over M1 leads to changes in ipsilateral SIHI exclusively without altering LIHI [24].

The findings presented indicate that SI modifies IHI in the bilateral motor cortex, although there remain some limitations to consider. In the present study, cTBS was applied over left-hemisphere SI in right-handed individuals. It remains unclear whether IHI exhibits hand-dominance specificity, with studies suggesting that hand dominance

does have an effect on IHI [1], whereas others suggest that it does not [2]. Therefore, it is difficult to predict the results after application of cTBS over right-hemisphere SI in right-handed individuals. A second consideration is whether other plasticity inducing repetitive TMS paradigms such as intermittent TBS (iTBS) would modify IHI when applied over SI. MEPs are facilitated for up to 15 min after application of iTBS over M1, whereas MEPs are suppressed for 60 min after cTBS application [25]. Therefore, one possibility is that iTBS would elicit a trend in the opposite direction to the findings presented here, resulting in decreased IHI.

3.5 CONCLUSION

The findings presented here indicate that SI can indeed alter IHI in the bilateral motor cortex. These findings, combined with those seen after application of cTBS over higher-order somatosensory area 5 [12], suggest one mechanism by which somatosensory cortices participate in the control of single-handed and dual-handed movements. Overall, the data suggest that SIs have the ability to modify motor output, and possibly behaviour, which may prove relevant in rehabilitative programs for individuals who exhibit deficiencies in the control of hand movements, possibly due to impaired IHI.

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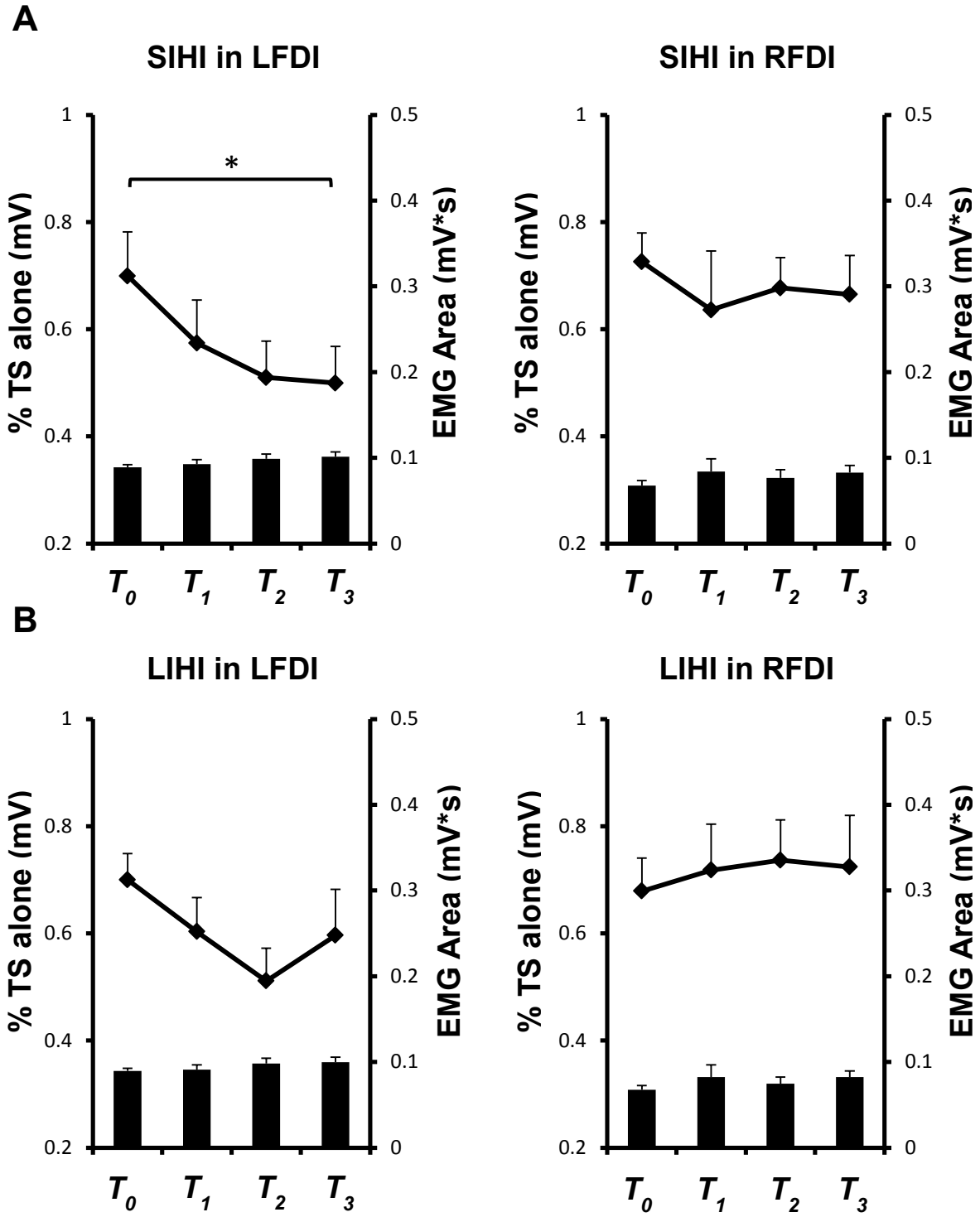

Figure 3.1. A. Group-averaged MEP amplitude normalized to TS alone for SIHI in left (left) and right (right) FDI muscles (with standard errors) recorded before and at each time block following cTBS applied over left-hemisphere SI. Area of pre-stimulus EMG is depicted by the black histogram for each time block. B. Group-averaged MEP amplitude normalized to TS alone for LIHI in left (left) and right (right) FDI muscles with standard error recorded before and at each time block following cTBS applied over left-hemisphere SI. Area of pre-stimulus EMG is depicted by the black histogram for each time block. Asterisks indicate Bonferroni corrected paired t-test with significance set at $p \leq 0.025$.

	T_0	T_1	T_2	T_3
LFDI				
CS	1.05 (0.28)	0.90 (0.17)	1.09 (0.30)	1.03 (0.22)
TS	0.98 (0.25)	0.94 (0.22)	1.19 (0.23)	1.15 (0.26)
RFDI				
CS	1.02 (0.24)	1.11 (0.26)	1.10 (0.28)	1.05 (0.24)
TS	1.11 (0.25)	1.08 (0.33)	1.04 (0.28)	0.96 (0.23)

Table 3.1. Group-averaged test stimulus and conditioning stimulus alone for each time block (mean ± SD). Repeated measures ANOVA revealed no significant difference between either TS alone or CS alone values. LFDI, left first dorsal interosseous muscle; RFDI, right first dorsal interosseous muscle; CS, conditioning stimulus; TS, test stimulus.

Chapter 4: Experiment 2

Effects of somatosensory inputs on SIHI

4.1 INTRODUCTION

The control of single and dual handed movements is a highly orchestrated process thought to be controlled by a disperse somatosensory network which includes primary motor (M1) and somatosensory cortices (SI) [101,102]. One mechanism involved in the control of hand movement is called interhemispheric inhibition (IHI) [103,104]. IHI is a neurophysiological mechanism that allows one M1 to inhibit neural activity in the homologous motor representation in the contralateral M1 leading to decreases in motor output from that hemisphere [6,7,9,11,57]. In healthy individuals, performance of a one-handed task leads to increases in IHI in the opposite relaxed hand and this is thought to prevent unwanted or mirror movements of the uninvolved hand [12]. The magnitude of this increase in IHI from the active task hand to the relaxed non-task hand is also directly related to the amount of mirror movement in the non-task hand, such that greater levels of IHI are associated with less mirror activity in the relaxed hand [105]. Conversely, IHI may also be decreased in the non-task hand and is suggested to allow for rapid engagement of that hand should the task require it [13], as supported by evidence from individuals with callosal agenesis [9] and subcortical and cortical lesions [55]. Data from healthy populations also support this view; minimal or absent IHI is seen in children [106] and is suggested to emerge with callosal myelination throughout childhood development [106,107].

IHI can be tested using a paired pulse transcranial magnetic stimulation (TMS) paradigm in which one TMS pulse, called the conditioning stimulus (CS), is applied to one M1 and precedes a second test stimulus (TS) applied to the contralateral M1 at latencies between 6 and 50 ms [6,7,16,57]. The CS is thought to activate excitatory transcallosal neurons that synapse onto populations of local inhibitory interneurons in the opposite M1, resulting in inhibition of cortical excitability in that hemisphere, and thus a decrease in the amplitude of motor output induced by the TS pulse [6,7,16,57]. The degree or "depth" of inhibition of motor output relates to the magnitude of the CS, with CS pulses of greater intensity resulting in greater inhibition of the opposite hemisphere [16]. IHI has been shown to act in two phases, a short interval inhibitory phase (SIHI) and a long interval inhibitory phase (LIHI), suggested to be mediated by $GABA_A$ [61,62] and $GABA_B$ [58-60]. In monkey species, disruptions to neural populations within SI and somatosensory afference impairs gross [98] and fine motor control [94]. Similarly, in humans, SI is important for the control of single and dual handed movements such as bimanual tracing [108-110]. Altering cortical activity within SI using continuous theta burst stimulation (cTBS), a form of repetitive TMS, over SI or higher order somatosensory area 5 increases IHI in the ipsilateral hand, that is, the hand ipsilateral to the CS [70,111]. Alterations in peripheral afferent input also modulate IHI. Ischemic nerve block of the arm decreases IHI measured in the occluded hand [71]. Muscle belly vibration increases IHI measured in the non-vibrated hand [72]. In stroke patients, anaesthesia applied to the non-paretic hand results in increases in task performance of the paretic hand [112], possibly due to changes in IHI as suggested elsewhere [25]. These findings are significant as some patient

groups who exhibit altered IHI, such as Parkinson's disease [24], dystonia [23], multiple sclerosis [113], and stroke [25,103,114] may also present with somatosensory abnormalities (Parkinson's: [24,115]; Dystonia: [23,115]; Multiple Sclerosis: [113]; Stroke: [25,103,114]), possibly implicating SI as a key contributor to the control of interhemispheric mechanisms.

The present study examines the influence of somatosensory afferent input evoked by peripheral nerve stimulation on IHI. When peripheral nerve stimulation is applied at a short latency (~20 ms) prior to a single TMS pulse an inhibition of the M1 contralateral to the origin of the somatosensory input is seen [73]. Similar to IHI, the level of inhibition is directly dependent on the intensity of the conditioning stimulus, in this case nerve stimulation, such that greater intensities yield greater levels of motor output inhibition [116,117]. It has previously been shown that somatosensory inputs arising from cutaneous and mixed nerve sources may result in different degrees of inhibition, with greater inhibition resulting from mixed nerve stimulation [118,119]. Further, following immobilization of the arm, application of vibro-tactile cutaneous stimulation, or no stimulation, increases IHI and decreases M1 excitability in the hemisphere contralateral to the immobilized hand, while the presence of proprioceptive inputs, such as those activated via mixed nerve stimulation, maintains IHI and M1 excitability at pre-immobilization values [120]. However, cutaneous nerve sources may exhibit somatotopic effects, where stimulation of one finger results in selective inhibition at the cortex of that finger only, while mixed nerve sources do not [121,122], possibly suggesting greater involvement of somatosensory cortical loci for the processing of these inputs. Thus, it is

possible that somatosensory inputs of different origins may alter IHI differently. It has previously been shown that electrically evoked mixed, median nerve somatosensory inputs may modify SIHI when applied at short [75] and long latencies [76]. However, it is unknown whether somatosensory inputs arising from a cutaneous source, such as the digital nerve of the index finger, would produce similar results to those from a mixed nerve source, such as the median nerve. Such information would offer insight into the neural circuitry modulating somatosensory inputs on cortical excitability and motor output to the hand.

Previous work investigating the effects of somatosensory inputs on IHI are exclusive to somatosensory inputs applied to the hand in which IHI is measured, that being, the hand contralateral to the TS hemisphere. However, evidence suggests that inputs applied contralateral to the CS hemisphere may also be able to modify IHI. At the cortical level, changes in the physiology of one SI may result in changes of the opposite SI. Following application of cTBS over left SI, changes in hemoglobin concentrations are seen in bilateral SI and M1, indicative of changes in neural excitability [77]. Further, following application of cTBS over SI or somatosensory area 5, changes in bilateral motor excitability are observed [78,123]. At the level of the periphery, vibration of the muscle tendons of one hand results in increased motor output from the M1 ipsilateral to vibration [72], denervation of one hand results in increased excitability of the ipsilateral M1 [71], and application of cutaneous anaesthesia to the non-paretic hand in chronic stroke patients results in marked improvements in task performance of the paretic hand [112]. This

evidence suggests that somatosensory inputs originating in the hand contralateral to the CS hemisphere may indeed be able to modify IHI in the opposite hand.

The purpose of the present study was to determine how mixed and cutaneous nerve inputs alter SIHI. IHI was evoked in the left hand at two different depths as defined by CS intensity, and the effects of two different nerve stimulation intensities were examined at each depth of IHI. Our previous studies have demonstrated that changes in IHI are found only in the hand ipsilateral to the hemisphere receiving cTBS [70,111]. Therefore, in the present study, nerve stimulation was applied ipsilateral and contralateral to the CS allowing a more comprehensive view of how somatosensory inputs from either hand may be used to alter IHI. Three hypotheses were made: 1) stronger peripheral inputs will result in greater reductions in IHI than weaker inputs of the same nerve composition; 2) stimulation of the mixed, median nerve will result in greater reductions in IHI than stimulation of the cutaneous digital nerve when comparing across an intensity, similar to the effects seen on motor excitability [118,119]; and 3) application of nerve stimulation to the hand contralateral to the CS side will result in decreased IHI. These findings would be significant for possible rehabilitation strategies in disease states such as stroke, dystonia, and Parkinson's disease, where losses in somatosensory function and abnormal levels of IHI may account for many symptoms associated with the disease.

4.2 METHODS

4.2.1 Participants

Seventeen individuals participated (8 male, mean age ± SD = 21.9 ± 2.23, range: 19 - 27). All participants were right handed as determined using an adapted subset of the Edinburgh Handedness Inventory [124]. Written informed consent was obtained from all participants prior to testing. This experiment conformed to the Declaration of Helsinki and was approved by the Research Ethics Board at McMaster University.

4.2.2 Electromyography (EMG)

Muscle activity of the first dorsal interosseous (FDI) muscles of both the left and right hands were recorded using surface electrodes (9 mm Ag-AgCl) placed in a muscle belly – joint montage with the active electrode placed over the muscle belly and the reference electrode over the metacarpophalangeal joint. EMG was then amplified 1000 x and filtered from 20-2500 Hz (Intronix Model 2024F, Intronix Technologies Corporation, Bolton, Canada). EMG was acquired using Signal software and an analog-to-digital converter (Power 1401, Cambridge Electronic Design, Cambridge, UK).

4.2.3 Interhemispheric Inhibition (IHI)

IHI consisted of applying a single conditioning pulse (CS) to the FDI motor representation in left M1followed by a single test pulse (TS) applied to the homologous

muscle representation in right M1 at a short interstimulus interval of 10 ms to elicit short latency interhemispheric inhibition (SIHI) [6,7,57]. TMS was applied using two custom built figure-of-eight branding coils (50 mm inner diameter) connected to three Magstim 200^2 units, with two units connected via a BiStim module (Magstim, Whitland, UK). FDI motor hotspots, defined as the optimal location for eliciting motor evoked potentials (MEP) in the contralateral FDI when the TMS coil was placed at a 45º angle to the mid-sagittal line, were located for both hemispheres and marked using Brainsight Neuronavigation software (Rogue Research, Montreal, Canada). IHI was measured in the left FDI muscle (left-to-right inhibition). As the depth of IHI is largely dependent on the intensity of the CS and TS [16], the CS intensity was set to elicit MEPs of peak-to-peak amplitude of 0.5 and 1 mV while the TS intensity was maintained to evoke MEPs of 1 mV in amplitude to allow two different depths of IHI to be investigated. Both CS intensities were tested synchronously using the aforementioned two Magstim 200^2 units connected by the BiStim module, while the TS was applied using a single Magstim 200^2 unit. Throughout the experiment, TS and CS intensities were monitored by individual conditions within each block wherein TS or CS pulses alone were applied and averaged to maintain the desired intensity.

4.2.4 Peripheral somatosensory stimuli

The median nerves were electrically stimulated using a bar electrode (200 μs, square wave pulse) with the anode placed distal over the wrist approximately 8 cm proximal to

the thenar muscles. The digital nerves were stimulated using ring electrodes (200 μs, square wave pulse) placed on the intermediate and proximal phalanxes of the index fingers with the anode located distally. For both types of nerve stimulation two intensities of stimulation were used, a "weak" stimulation at 1.5 x sensory perceptual threshold (ST) and a "strong" stimulation at 3 x ST, as individually determined for that type of stimulation, where ST was defined as the lowest intensity stimuli barely discernible by the participant with eyes closed and no external distractions. Sensory perceptual thresholds were determined immediately prior to data collection, and were checked following half of the data collection. Stimuli were applied to either left or right hand such that arrival at M1 was timed to correspond with the TMS pulse from the TS or CS, respectively. For median nerve, stimuli were applied 22 ms prior to the TMS pulse of interest, while for the digital nerve, stimuli were applied 25 ms prior to the TMS pulse of interest, latencies described elsewhere as optimal values for eliciting afferent inhibition of a TMS pulse applied over the contralateral motor cortex [116,118].

4.2.5 Data Collection

Data was collected in four blocks of 100 trials with each block differing by the nerve stimulated (i.e. median or digital) and the intensity of nerve stimulation (i.e. 1.5 x or 3.0 x ST) present for that block. Each block was then sub-sectioned into two sub-blocks to aid in subject fatigue. The order of the 4 blocks were counterbalanced across participants.

Within each block IHI was investigated such that ten repeats of each condition (A – J conditions, Table 4.1) were presented randomly.

4.2.6 Data Analysis

MEP peak-to-peak amplitudes for conditions which represent IHI with no nerve stimulation (E and F) were normalised to the unconditioned TS alone condition (A) for each block. MEP amplitudes for conditions which represent IHI with nerve stimulation applied contralateral to either the TS or CS hemispheres (G,H, I and J) were normalised to the unconditioned TS alone condition for each block, as used in previous studies [75,76]. For conditions E - J normalised values of less than 1 represent inhibition while values greater than 1 represent facilitation of corticospinal output. Only participants who exhibited MEP amplitude ratios of < 1 for conditions E and F (i.e. exhibited IHI) were included in all further analyses. Formulae used to calculate MEP amplitude ratios are depicted in Figure 4.1.

Two analysis methods were performed. In analysis 1, four one-way repeated measures ANOVA were performed on MEP amplitude ratios determined for each condition listed above using within subject factor CONDITION (5 levels; IHI alone, Weak MNS, Strong MNS, Weak DNS, Strong DNS) with one ANOVA being performed for each combination of level of IHI (low or high) and site of nerve stimulation (contralateral to TS or CS). In analysis 2, four one-way repeated measures ANOVA were performed on differential values obtained by subtracting the respective level of IHI alone from the MEP

amplitude ratio for each condition, which results in a value representing the absolute change in level of inhibition in millivolts. ANOVAs were performed with one ANOVA being performed for each combination of level of IHI and site of nerve stimulation with within subject factor CONDITION (4 levels; Weak MNS, Strong MNS, Weak DNS, Strong DNS). Post-hoc Tukeys HSD test was used to determine significant differences in the means where a significant F-statistic was observed. Bonferroni corrected *a priori* t-tests were used to test all hypotheses. Statistical significance was set at $p \leq 0.05$.

4.3 RESULTS

All participants successfully completed the experiment. Data from two participants was removed as they did not meet the IHI criteria (i.e. IHI alone MEP amplitude ratios were > 1). All analyses were subsequently performed on data from the remaining 15 participants (6 male, mean age ± SD = 22.1 ± 2.31, range: 19 - 27). Table 4.2 displays group-averaged MEP amplitudes for TS, $CS_{0.5mV}$, and $CS_{1.0mV}$.

Group-averaged data for all conditions for Analysis 1 is displayed in Figure 4.2. One way repeated measures ANOVA for IHI Low with NS Contralateral to TS revealed a significant effect of CONDITION ($F_{(4,56)} = 3.67$, $p = 0.010$). One way repeated measures ANOVA showed no significant effect of CONDITION for IHI High with NS Contralateral to TS ($F_{(4,56)} = 1.53$, $p = 0.21$), IHI Low with NS Contralateral to CS ($F_{(4,56)} = 0.84$, $p = 0.51$), or IHI High with NS Contralateral to CS ($F_{(4,56)} = 0.51$, $p = 0.73$). Post-hoc Tukeys HSD test was performed on the significant IHI Low with NS Contralateral to

TS and revealed that the Strong MNS condition was significantly different as compared to both the IHI alone and Weak MNS conditions. To test *a priori* hypotheses Bonferroni corrected t-tests were performed. For inputs applied contralateral to the TS significance was Bonferroni corrected to $p \leq 0.0125$ due to four comparisons being made. For inputs applied contralateral to the CS significance was Bonferroni corrected to $p \leq 0.01$ due to five comparisons being made. For hypothesis 1, that stronger peripheral inputs will result in greater reductions in IHI than weaker inputs of the same nerve composition, a two-tailed Bonferroni corrected t-tests were used as the direction of the hypothesis was incorrect. T-tests revealed no significant difference between median or digital nerve stimulation for IHI Low with NS Contralateral to TS (MNS: p-value = 0.0324, DNS: p-value = 0.80), IHI High with NS Contralateral to TS (MNS: p-value = 0.24, DNS: p-value = 0.22), IHI Low with NS Contralateral to CS (MNS: p-value = 0.53, DNS: p-value = 0.19), or IHI High with NS Contralateral to CS (MNS: p-value =0.46, DNS: p-value = 0.46). For hypothesis 2, that stimulation of the mixed, median nerve will result in greater reductions in IHI than stimulation of the cutaneous digital nerve when comparing across an intensity, two-tailed Bonferroni corrected t-tests were used as the direction of the hypothesis was incorrect and revealed no significant difference between median or digital nerve stimulation for IHI Low with NS Contralateral to TS (Low: p-value = 0.24, High: p-value = 0.11), IHI High with NS Contralateral to TS (Low: p-value = 0.70, High: p-value = 0.96), IHI Low with NS Contralateral to CS (Low: p-value = 0.92, High: p-value = 0.43), or IHI High with NS Contralateral to CS (Low: p-value = 0.92, High: p-value = 0.84). For hypothesis 3, that peripheral inputs applied contralateral to the CS hemisphere

would result in decreases in IHI, all conditions in which nerve stimuli were applied contralateral to the CS hemisphere were pooled into one bin to test the effects of any peripheral input applied contralateral to the CS hemisphere on IHI. A two tailed Bonferroni corrected t-test was used as the direction of the hypothesis was incorrect and revealed no significant differences for either Low IHI (p-value = 0.41) or High IHI (p-value = 0.31).

Group-averaged data for all conditions for Analysis 2 is displayed in Figure 4.3. One way repeated measures ANOVA for IHI Low with NS Contralateral to TS revealed a near significant effect of CONDITION ($F_{(3,42)} = 2.68$, $p = 0.059$). One way repeated measures ANOVA showed no significant effect of CONDITION for IHI High with NS Contralateral to TS ($F_{(3,42)} = 1.21$, $p = 0.32$), IHI Low with NS Contralateral to CS ($F_{(3,42)} = 0.88$, $p = 0.46$), or IHI High with NS Contralateral to CS ($F_{(3,42)} = 0.47$, $p = 0.71$).

4.4 DISCUSSION

In the present study, we investigated the effects of differing contents and intensities of peripheral somatosensory inputs on multiple depths of left-to-right SIHI. Further, the effects of these somatosensory inputs from both hands on left-to-right SIHI were examined. Novel findings of this study are that when applied contralateral to the TS hemisphere, strong mixed content somatosensory inputs may significantly increase IHI when applied at a low level of IHI, while application of weak mixed inputs and both weak and strong cutaneous inputs resulted in similar, yet modest, increases in inhibition.

Further, when applied contralateral to the CS hemisphere, IHI remains largely unchanged regardless of the strength or content of the input as well as the baseline level of IHI. These results indicate that somatosensory inputs are indeed able to alter IHI and that the effect is at least partly based upon the content and strength of the input.

Following application of somatosensory inputs contralateral to the TS hemisphere it was found that when applied at a weak level of IHI strong mixed content inputs resulted in significant increases in IHI as compared to IHI without nerve stimulation and IHI with weak mixed content nerve stimulation. Application of weak or strong cutaneous inputs, as well as weak mixed inputs similarly resulted in increases in IHI, although the effects were more modest. At a high level of IHI no significant effects were seen although a similar trend of increased IHI for all somatosensory inputs, regardless of content or strength, was seen. This is in contrary to the results of a previous study which suggested that mixed content inputs could only alter SIHI when applied at a strong intensity and at a high level of IHI, with no effects being seen when applied at a low level of IHI [75]. Further, this study found that somatosensory inputs applied contralateral to the TS hemisphere result in decreased IHI [75] , rather than the increased IHI seen in the present study. While perplexing at first as to how two very similar paradigms could result in such drastically different results, some differences between the methodologies of the two studies exist which may explain the differences. First, in the study by Tsutsumi et al. [75] a TS amplitude of 0.6 mV was used, as compared to the 1 mV measure used in the present study. It is possible that the relatively low TS amplitudes used in the study by Tsutsumi et al. [75] in some way caused the differences in effects observed. Indeed it may be that in

the current study effects on low and high threshold corticospinal neurons are being investigated while the previous study investigated the effects on low threshold corticospinal circuitry only. Another point of difference is the CS intensities used. In the present study, the intensity of the CS pulse is determined as the necessary stimulator output to elicit a 0.5 mV or 1.0 mV MEP in the right hand when applied alone. In the previous study by Tsutsumi et al. [75] however, CS intensity was set as a percentage of RMT. There are two possible points of differentiation on this matter. One is that effects in the previous study were observed only at "high" levels of IHI as indicated by CS intensities of 1.2 and 1.4 times RMT. While a value of 1.2x RMT has been previously suggested to equate to a value of approximately 1.0 mV [125], this is frequently not the case. It is possible that the depth of IHI investigated in the previous study is in fact either much stronger or much weaker than suggested, possibly resulting in drastically different results than were observed in the present study. A second point of differentiation over the CS intensities is that in the previous study by Tsutsumi et al. [75], CS values were determined as a percentage of RMT at the beginning of the experiment and were maintained at that percentage of maximum stimulator intensity for the remainder of the experiment. This is an issue as throughout the study, cortical excitability may change due to a number of factors, such as degree of wakefulness [126,127] and fatigue [128], and this is not controlled for in the study by Tsutsumi et al [75]. However, in the present study the intensities of the two CS pulses are maintained throughout the experiment using a measure which is also dependent on the current state of cortical excitability, thus accounting for changes in cortical excitability due to changes in the level of arousal. One

final source of differentiation between the study by Tsutsumi et al. [75] and the present study is the population investigated. In the present study, the population investigated was healthy young adults (mean age ± SD = 21.9 ± 2.23) while the previous study by Tsutsumi et al. [75] investigated an older healthy population (mean age ± SD = 37.5 ± 7.8 years old). IHI has previously been shown to change with age [129] so it is possible that the difference in effects seen between these two studies may in fact be due to differences in the populations tested.

This study is the first to investigate the effects of somatosensory inputs applied contralateral to the CS on IHI. However, it has previously been shown that alterations in access to somatosensory input in one hand results in changes in the motor output to the opposite hand. Following denervation of one hand, increased excitability of the ipsilateral M1 is seen [71]. Further, muscle tendon vibration of one hand results in increases in motor output measured in the opposite hand [72]. Finally, following application of cutaneous anaesthesia to the non-paretic hand in chronic stroke patients, improved performance of unilateral motor tasks is seen in the paretic hand [112]. However, in the present study somatosensory inputs applied contralateral to the CS hemisphere had no significant effect on IHI, and thus motor output to the hand opposite to the origin of the somatosensory inputs. The lack of effects seen could be due to a number of reasons. One is that perhaps an input of stronger intensity is required to elicit changes in IHI or motor output of the opposite hemisphere. Another is that perhaps the input is regarded as "irrelevant" to the task at hand and thus is gated either prior to, or, at arrival to SI [130]. Sensory gating has previously been suggested to be implicated with interhemispheric

mechanisms, as following application of a task-relevant cutaneous stimuli changes in blood flow of the ipsilateral motor cortex surrounding the homologous motor representation are seen [131], an effect suggested elsewhere to possibly be due to IHI [130]. Thus this may be the more likely reason as to why no effect was observed in the present study for inputs applied contralateral to the CS hemisphere.

Previously, it has been shown that median nerve inputs alter IHI in an intensity dependent fashion, where stronger peripheral inputs result in greater changes in IHI [75] . A similar trend also holds true when examining the effect of afferent inputs on motor output [116]. In the present study we found that, when comparing across nerve type, IHI was similarly altered to a greater extent by strong than weak inputs regardless of the content of the input or the level of IHI at which the inputs were applied. However, this trend only held true for inputs applied contralateral to the TS hemisphere. When applied contralateral to the CS hemisphere, weak inputs appear to result in decreased IHI while strong inputs resulted in increased IHI. It is possible that weak inputs activate a different set of circuitry than strong inputs resulting in this difference, however, due to the statistical insignificance of these findings all observations on this matter are pure speculation.

Previously, it has been shown that both SIHI and LIHI are modified via application of somatosensory afferent inputs from the mixed median nerve [75,76] . We now extend these findings to show that SIHI may also be mediated by somatosensory afference originating from cutaneous inputs, as at a high level of IHI strong cutaneous inputs resulted in a similar level of increased inhibition as that seen by strong mixed sources.

However, at a weak level of IHI, cutaneous inputs result in relatively modest increases in IHI.

Similar to the effects of somatosensory inputs on motor output measured via a single TMS pulse, mixed nerve inputs usually resulted in greater changes in motor excitability than similar input derived from cutaneous nerve sources [118,119], when comparing across "low" versus "high" nerve stimulation intensity conditions in the present study. It is possible this is due to an increased volume of input following stimulation of a mixed versus cutaneous nerve, as suggested elsewhere [118,121]. However, it is also possible that mixed afferent input is more relevant to the function of IHI (i.e. control of single and dual handed movements) and thus results in a greater effect. This would not be surprising, as proprioceptive feedback has been shown to be important for the maintenance of normal levels of M1 excitability and IHI following arm disuse, while cutaneous inputs are not [120]. Further, from an anatomical perspective, it would not be surprising that proprioceptive cues are more able to alter motor output based purely upon cytoarchitectural connections between M1 and each sub-area of SI. All areas of SI, with the exception of Brodmann area 3b, possess direct connections to M1 [19,21,22], and each area is responsible for processing of different types of inputs. Specifically, area 3a is responsible for processing of deep tissue and muscle afferents [21,92], while area 3b is responsible for processing of mainly cutaneous inputs [92]. Therefore, as area 3a possesses direct connectivity to M1 and processes mainly proprioceptive inputs while 3b does not have direct connectivity to M1 and processes predominantly cutaneous inputs, it

is perhaps not surprising that larger reductions in IHI are seen for mixed, median nerve inputs than those from the cutaneous, digital nerve.

One possible limitation to the present work is that IHI was measured in the left-to-right direction only. The depth of IHI between dominant and non-dominant hemispheres has been suggested to differ depending on the direction measured, with the dominant hemisphere suggested to inhibit the non-dominant hemisphere to a greater extent than vice-versa, however this is not unanimous. Some studies have shown these hand-dominance effects [63,64] while others have not [13,65]. Therefore, a future direction for this research would be to extend these findings to investigate the effects of differing contents and intensities of peripheral somatosensory inputs on IHI when measured from the non-dominant to dominant hemisphere. This would provide valuable insight into whether somatosensory inputs have differing effects depending on the direction of IHI, as well as whether somatosensory afference is processed differently from the dominant or non-dominant hand.

4.5 CONCLUSION

In the present study we investigated the effects of differing intensities and contents of peripheral somatosensory afferent input on multiple depths of unidirectional left-to-right SIHI. Further, we also investigated how input from both hands would affect this neural mechanism. The findings here further the understanding of how somatosensory inputs alter motor outputs, as well as how sensory inputs alter neural mechanisms, in this case

SIHI. Specifically, these findings suggest that somatosensory inputs are indeed able to alter SIHI, and that the degree of influence is largely dependent on the content and intensity of the somatosensory input. These findings may one day be used to aid in the rehabilitation of many movement and neurologic disorders which present with abnormal levels of IHI as well as somatosensory impairments.

Condition	Description
A	TS Alone
B	CS low alone
C	CS high alone
D	TS with nerve stimulation (NS)
E	IHI low (CS low)
F	IHI high (CS high)
G	IHI low (NS contralateral to TS)
H	IHI high (NS contralateral to TS)
I	IHI low (NS contralateral to CS)
J	IHI high (NS contralateral to CS)

Table 4.1. Summary of experimental conditions tested.

$$IHI = \left(\frac{TS_{CS}}{TS} \right)$$

$$IHI_{NS} = \left(\frac{(TS_{CS})_{NS}}{TS} \right)$$

Figure 4.1. Formulae used to determine MEP amplitude ratios. Subscripts represent conditioning effects on the TS pulse.

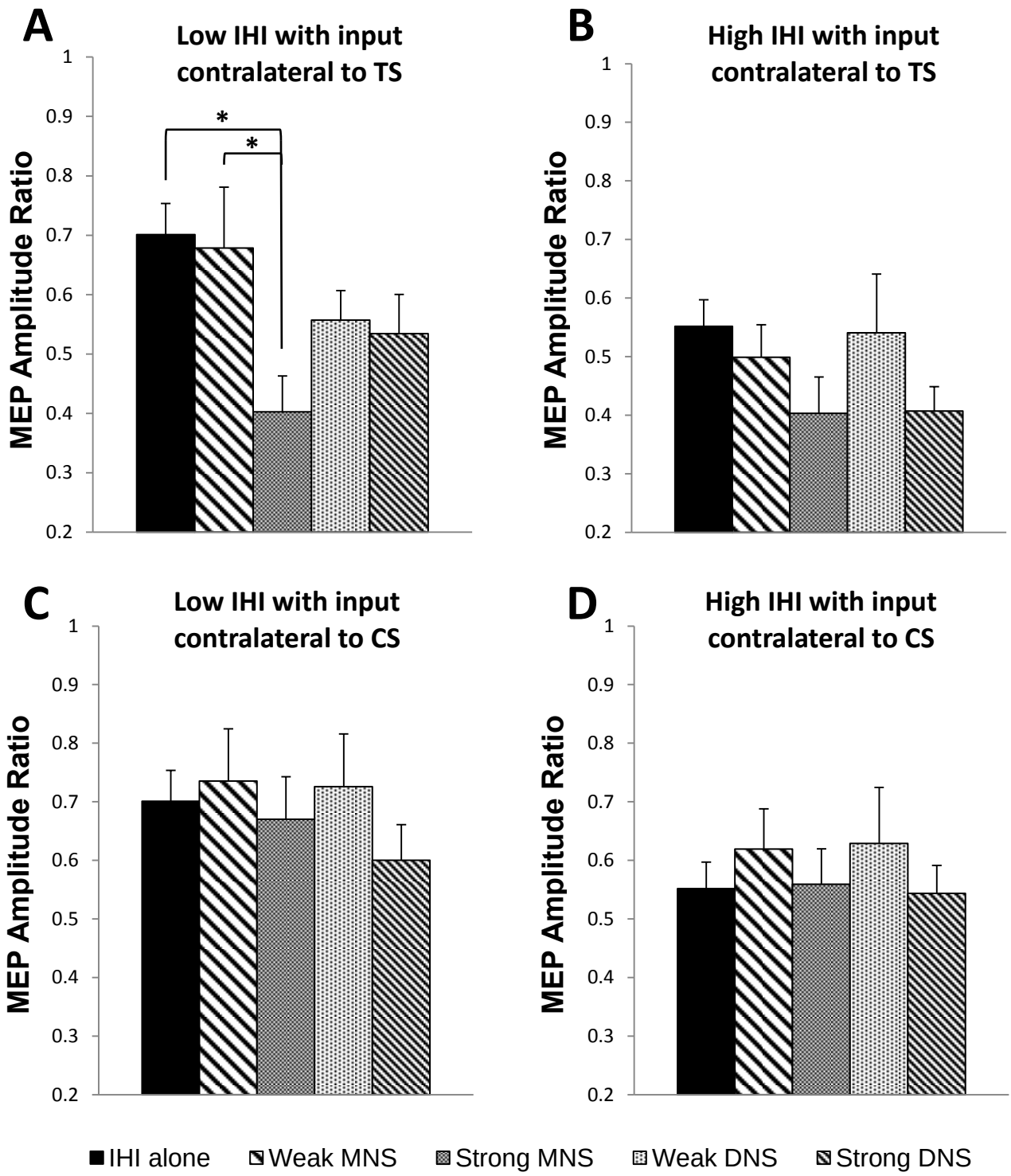

Figure 4.2. A. Group averaged MEP amplitude ratios for Weak MNS, Strong MNS, Weak DNS, and Strong DNS for: A. Low IHI with NS contralateral to TS. B. High IHI with NS contralateral to TS. C. Low IHI with NS contralateral to CS. D. High IHI with NS contralateral to CS. Asterisks indicate significant difference between the means with significance set at $p \leq 0.05$.

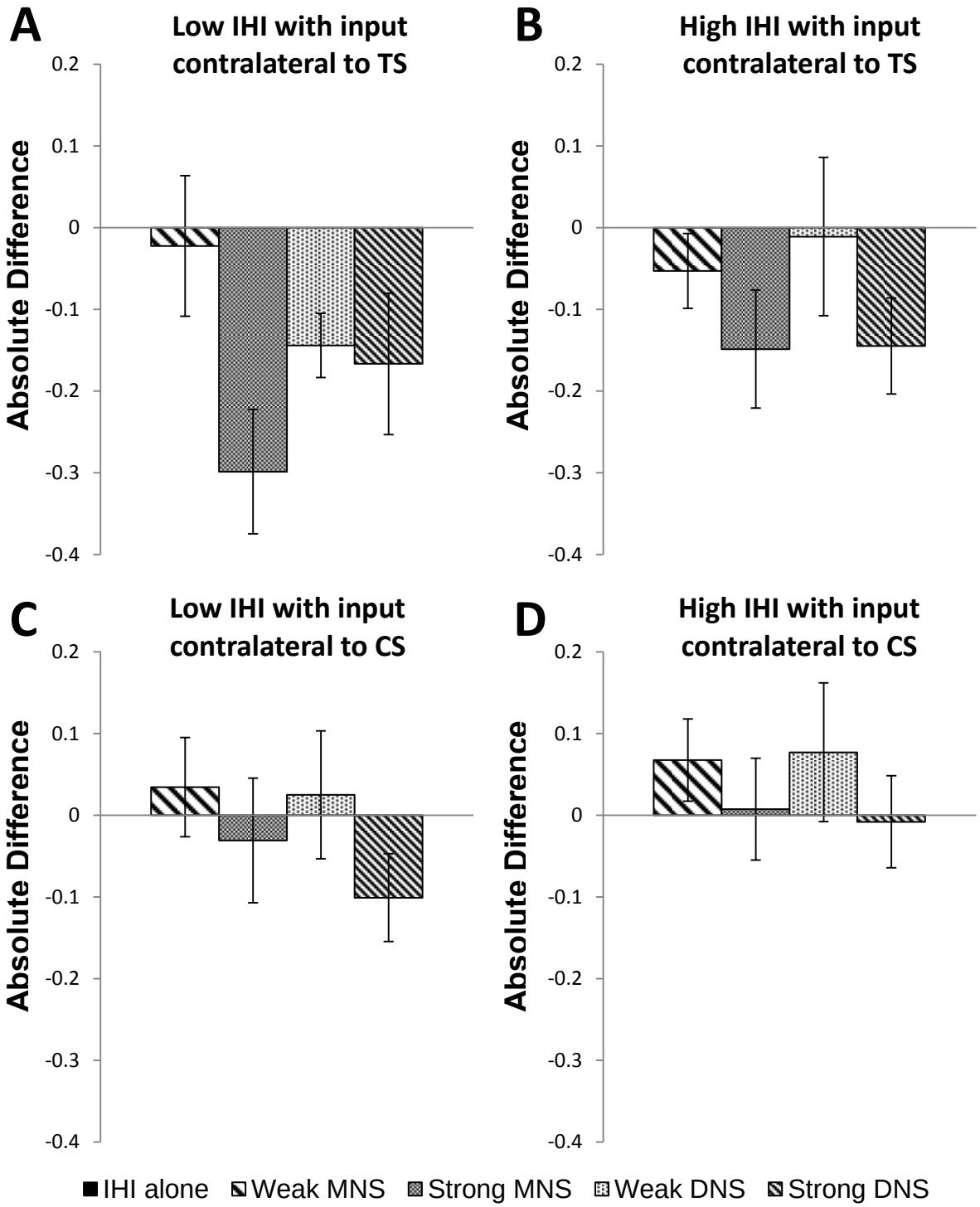

Figure 4.3. A. Group averaged absolute difference of MEP amplitude ratios to IHI alone for Weak MNS, Strong MNS, Weak DNS, and Strong DNS for: A. Low IHI with NS contralateral to TS. B. High IHI with NS contralateral to TS. C. Low IHI with NS contralateral to CS. D. High IHI with NS contralateral to CS. Values > 0 represent reduced IHI, values < 0 represent increased IHI. Asterisks indicate significant difference between the means with significance set at $p \leq 0.05$.

	Weak MNS	***Strong MNS***	***Weak DNS***	***Strong DNS***
$TS_{1.0\,mV}$	1.09 (0.28)	1.08 (0.20)	1.13 (0.26)	1.20 (0.41)
$CS_{0.5\,mV}$	0.77 (0.34)	0.65 (0.19)	0.67 (0.20)	0.66 (0.21)
$CS_{1.0\,mV}$	1.28 (0.35)	1.20 (0.22)	1.17 (0.38)	1.11 (0.31)

Table 4.2. Group-averaged test stimulus and conditioning stimulus alone for each condition (mean ± SD). Repeated measures ANOVA revealed no significant difference between either TS alone or CS alone values. CS, conditioning stimulus; TS, test stimulus.

Chapter 5: General Discussion

The goal of this thesis was to investigate the role of primary somatosensory cortex in the control of interhemispheric inhibition between bilateral primary motor cortex. To elucidate this relationship, two experiments were performed in right handed individuals to examine the direct cortical control which SI exhibits over IHI as well as the processing of peripheral somatosensory inputs on IHI. Experiment 1 investigated the influence of SI on bi-directional SIHI and LIHI before and after application of cTBS over left hemisphere SI. Experiment 2 investigated the influence of different intensities and contents of somatosensory inputs on two depths of left-to-right SIHI (i.e. in the left hand). SI was chosen as a possible cortical locus by which IHI may be modulated as many neurological and movement disorders which present with somatosensory abnormalities, possibly due to impairments in SI activity, also present with abnormal levels of IHI (Dystonia:[23]; Multiple Sclerosis: [113]; Stroke: [25,103]; Parkinson's Disease: [24,115]). Thus, it seems likely that SI functioning is important for the control of IHI and thus offers a possible route for rehabilitative strategies. In Experiment 1, cTBS was utilized as it has previously been shown to alter neural activity over SI [43,78] as well as other higher order somatosensory areas [123]. In Experiment 2, electrical stimulation of the peripheral median and digital nerves was utilized to provide further information into how somatosensory afference is used to alter resting levels of IHI in typically functioning healthy adults. The findings from both experiments suggest that SI is able to modulate the short latency inhibitory phase of IHI (SIHI), while Experiment 1 suggests that this control

does not extend to the long latency inhibitory phase (LIHI). However, while both studies show a similar ability for SI to alter resting SIHI levels, Experiment 1 suggests changes largely in the ipsilateral hand, while Experiment 2 suggests changes largely in the contralateral hand, illustrating that SIHI in the left hand may be modulated by stimulation of left hemisphere SI and also by nerve stimulation delivered to the nerves of the left hand. A proposed mechanism which explains the findings of this thesis is displayed in Figure 6.5 and will be discussed in detail throughout the following discussion. As mentioned previously, these results hold importance to the understanding of disease mechanisms in many movement and neurological disorder patient groups as well as providing a better understanding of the neural circuitry which underpins IHI, specifically SIHI.

Previous work has investigated the effects of mixed, median nerve inputs applied at two intensities on differing depths of SIHI; however this work was limited to inputs applied contralateral to the TS hemisphere exclusively [75,76]. This thesis is the first to investigate the effects of mixed, median nerve inputs applied contralateral to the CS hemisphere of an IHI pairing on SIHI, as well as the first to investigate the effects of cutaneous, digital nerve inputs on SIHI when applied contralateral to either the TS or CS hemispheres of an IHI pairing. Further, this thesis is also the first to investigate the effects of a plasticity inducing rTMS paradigm applied directly over SI on IHI. Prior to this work, it was suggested that SI may be involved in the control of IHI as changes in excitability of somatic cortices, such as SI and area 5, results in increases in M1 motor output of the contralateral, non-stimulated hemisphere [78,123], possibly due to a release

of IHI from ipsilateral to contralateral M1. Further, following application of cTBS over area 5, increases in IHI in the hand ipsilateral to stimulation are seen [70], strengthening the idea that somatic cortices are involved in the control of IHI. Experiment 1 revealed that SI is indeed able to modify IHI between bilateral M1, such that following application of cTBS over left hemisphere SI, SIHI was increased in the ipsilateral (left) hand only. Further, cTBS applied over left hemisphere SI did not alter SIHI in the right hand, or LIHI bilaterally. These results suggest that cTBS applied over SI is able to specifically alter the depth of SIHI from ipsilateral-to-contralateral M1. Based on this finding, Experiment 2 focused on the effects of application of different intensities and contents of peripheral somatosensory inputs on SIHI when applied contralateral to the TS hemisphere, to investigate the effect of somatosensory inputs from the hand effected by TMS induced IHI, or contralateral to the CS hemisphere, to further elucidate the ipsilateral effects seen in Experiment 1. Three key findings were observed in Experiment 2; 1) strong mixed content somatosensory inputs are able to significantly increase SIHI when applied contralateral to the TS hemisphere at a low level of IHI. Increases in IHI were significantly greater than the levels of IHI measured when no nerve stimuli were presented or when IHI was measured in the presence of weak mixed nerve stimulation. Further, weak or strong cutaneous inputs resulted in only modest increases in IHI; 2) Strong mixed and cutaneous afferent inputs produced a similar level of increased IHI when applied at high levels of IHI. However, at low levels of IHI, mixed content inputs resulted in much greater increases in IHI than those elicited by cutaneous content inputs;

3) When applied contralateral to the CS hemisphere, little to no change in resting SIHI is seen regardless of level of IHI, strength of input, or content of input.

The proposed mechanism which explains the findings from Experiment 1 and 2 is explained in 3 segments; effects of direct changes in SI cortical excitability on IHI (Figure 6.2); effects of peripheral somatosensory afferent inputs applied contralateral to the TS hemisphere on IHI (Figure 6.3); and effects of peripheral somatosensory afferent inputs applied contralateral to the CS hemisphere on IHI (Figure 6.4). Further, Figure 6.5 depicts the overall mechanism by which SI may modulate IHI between bilateral M1. For all mechanisms, the well-established circuitry, as described previously, by which excitatory transcallosal projections originating in M1 synapse onto populations of inhibitory interneurons which control corticospinal output in that hemisphere is used as the basis for the mechanism and is simply expanded upon to explain the findings seen here. This circuitry is depicted in Figure 6.1.

5.1 Mechanism for modulation of SIHI via direct cortical stimulation

In Experiment 1, the effect of cTBS applied directly to left SI on bi-directional SIHI and LIHI was examined. Results show that SIHI ipsilateral to stimulation (i.e. left hand) was increased following cTBS, while SIHI in the contralateral right hand and LIHI bilaterally were unaltered. These results suggests a mechanism by which SI is able to selectively modulate activity of SIHI-modulating $GABA_A$ interneurons affecting SIHI in the left hand only, while not altering activity in LIHI-modulating $GABA_B$ interneurons. As

$GABA_A$ergic interneurons are associated with inhibitory effects, it seems likely that SI is able to alter SIHI via a $GABA_A$ mediated inhibitory projection which synapses onto the excitatory transcallosal connections in M1. Whether this increase in transcallosal excitability is elicited via disinhibition of an inhibitory mechanism, like the mechanism proposed previously, or via facilitation of an excitatory pathway is uncertain. Alternatively, as cTBS has been shown to elicit remote changes in cortical loci [132] it is possible that following cTBS $GABA_A$ergic activity in the TS hemisphere (i.e. contralateral to stimulation) is altered, resulting in increased inhibitory activity and that this is what drives the observed effects rather than changes in excitability of the excitatory transcallosal connections. However, as this experiment is not able to discern the exact neural pathway of this finding the results are depicted in Figure 6.2 as a general ability for SI to increase excitability in the excitatory transcallosal projections which mediate IHI, as this is the more likely mechanism due to other evidence suggesting changes in ipsilateral M1 excitability following cTBS applied over SI [78]. Regardless, the net effect of either of these mechanisms is an effective increase in activity of the transcallosal projections resulting in increased activity of the inhibitory interneuron populations in the opposite M1 and thus an increase in IHI, as measured via a decrease in the corticospinal motor output.

5.2 Mechanism for modulation of SIHI via application of peripheral somatosensory inputs contralateral to the TS hemisphere

In Experiment 2, the effects of peripheral somatosensory inputs applied contralateral to the TS hemisphere on SIHI were examined. Results showed that SIHI was significantly increased only when strong mixed content inputs were applied at a low level of IHI. At a high level of IHI strong inputs of both mixed and cutaneous origins resulted in similar, yet modest, non-significant increases in IHI. This is in contrast to the results of previous work [75], and while the reasoning for why differences in findings may have resulted was discussed previously, the specific mechanism by which strong mixed inputs may alter SIHI were not.

In order for somatosensory inputs to result in increased inhibition when applied contralateral to the TS hemisphere one of two options must occur; 1) excitability of the inhibitory interneurons governing IHI must be increased; or 2) excitability of the corticospinal outputs neurons must be decreased. Corticospinal output is elicited by summation of a series of descending volleys, or indirect waves (I-waves), which represent trans-synaptic activation of chains of corticospinal neurons [54]. Changes in these I-waves have been attributed to inputs from cortico-cortical mechanisms and local interneuronal populations onto the corticospinal output neurons [133], and it has been suggested that SIHI predominantly acts on the I-3 wave of this circuit while also minimally affecting I-2 waves and having no effect on I-1 waves [54]. Similarly, somatosensory inputs have been shown to inhibit motor output largely through inhibition of the I-3 and I-2 waves [73]. Thus the latter option seems more likely, as both inputs

have previous evidence to support this mechanism. However, as the results of Tsutsumi et al. [75] suggest that these two mechanisms utilize mutual inhibitory circuitry to inhibit motor output, the former option must still be considered as a possibility.

At a low level of IHI, strong mixed inputs were able to significantly increase IHI, while other inputs resulted in very modest increases in IHI. Further, at a high level of IHI strong mixed inputs resulted in increases in IHI of similar magnitudes to that seen at a low level of IHI (Low IHI: ~20%; High IHI: ~15%). However, while resulting in only modest increases in IHI when applied at a low level of IHI, at a high level of IHI strong cutaneous inputs resulted in increases in IHI to a level nearly identical to that of the strong mixed input (Strong mixed: ~15%; strong cutaneous: ~15%). One interpretation of this is that the inhibition of motor output via IHI is set upstream of that by the somatosensory input, likely at the I-3 wave generating interneurons, while the somatosensory input acts at a lower level, likely at the I-2 generating interneurons, to increase the level of inhibition as indicated by the somatosensory input and SI. Figure 6.3 depicts the most likely mechanism by which the results seen here are explained, however the specific level at which somatosensory inputs may alter the level of inhibition induced by IHI is not indicated as it is uncertain.

5.3 Mechanism for modulation of SIHI via application of peripheral somatosensory inputs contralateral to the CS hemisphere

In Experiment 2, the effects of peripheral somatosensory inputs applied to the hand contralateral to the CS hemisphere on SIHI where investigated. Results showed that afferent input applied contralateral to the CS hemisphere (right hand) resulted in no significant changes in IHI regardless of the level of IHI or the content and intensity of the somatosensory input. While results of inputs applied contralateral to the TS hemisphere suggest that somatosensory inputs can indeed alter SIHI, these effects do not seem to be replicable when inputs are applied contralateral to the CS hemisphere. This could be due to a number of reasons such as insufficient intensity of input to result in sufficient changes to the excitability of the transcallosal connections, or perhaps even sensory gating of the "task-irrelevant input".

5.4 Clinical Significance

As mentioned previously, many neurologic and movement disorders which present with somatosensory abnormalities also present with atypical levels of IHI (Dystonia: [23]; Multiple Sclerosis: [113]; Parkinson's Disease: [24,115]; Stroke: [25,103]). If the models presented here are in fact correct it would allow for a greater understanding of how somatosensory deficits in these patient groups may in fact be driving losses in unimanual and bimanual control via atypical levels of IHI, or alternatively, how application of cTBS or somatosensory inputs may be used as part of a rehabilitation plan in these individuals.

For example, patients diagnosed with schizophrenia have been shown to exhibit impaired IHI [26]. Using the proposed model, IHI could be increased by either of two methods; 1) cTBS applied over SI would result in increased IHI in the contralateral hand via increased excitability of the transcallosal connections originating in the M1 ipsilateral to stimulation and synapsing on inhibitory interneurons in the opposite hemisphere, as depicted in Figure 6.2; or, 2) application of strong mixed somatosensory input to the hand, a method not previously thought useful prior to the findings presented in this thesis. Application of somatosensory inputs to the hand would result in increased IHI towards the hemisphere contralateral to stimulation, due to increased inhibition of the motor output via a net inhibitory influence of peripheral inputs on IHI, resulting in return to levels of IHI nearer to those typical for a healthy individual. Further, both methods could be combined to provide increased IHI to both hands, allowing for improved control of both unimanual and bimanual tasks.

5.5 Limitations

These experiments, and the interpretation of the results, are not without their limitations. First, in Experiment 1, cTBS was applied over the dominant, left, hemisphere in right handed individuals, and based on those results, Experiment 2 focused on elucidating the effects seen in the left hand. However, some studies report differences in the depth of IHI from dominant to non-dominant hemispheres as compared to non-dominant to dominant [63,64]. Thus while no difference was seen for the present study between dominant to

non-dominant and non-dominant to dominant IHI, it is still possible that the effects following cTBS applied over the non-dominant right hemisphere SI would be different than those seen presently. Second, the exact way in which cTBS acts at the neuronal level is still unknown, thus inferences were made about the neural circuitry by which SI may modulate IHI and how cTBS may affect this circuitry. Third, the exact mechanism by which peripheral somatosensory inputs modulate motor outputs, and thus possibly IHI, are also not certain. While much evidence supports the idea that somatosensory afference modulates IHI via a short cortico-cortical loop via SI [21,134], it is also possible that the sensory inputs are directly relayed to M1 via the thalamus [135]. Thus, while extremely likely that these sensory inputs are relayed through SI to elicit inhibition in M1, it cannot be ruled out that these inputs may also exhibit direct influence onto M1 in some individuals.

5.6 Conclusions

This thesis is the first to investigate the influence of SI on IHI. This relationship was investigated in such a way as to further elucidate both the direct cortical influence of SI on IHI, as well as the indirect peripheral influence of somatosensory inputs on IHI. The findings of this thesis are directly relatable to certain clinical populations which exhibit atypical levels of IHI while also furthering the academic understanding of how SI may alter IHI functioning in healthy adult humans.

Chapter 6: Proposed Mechanisms

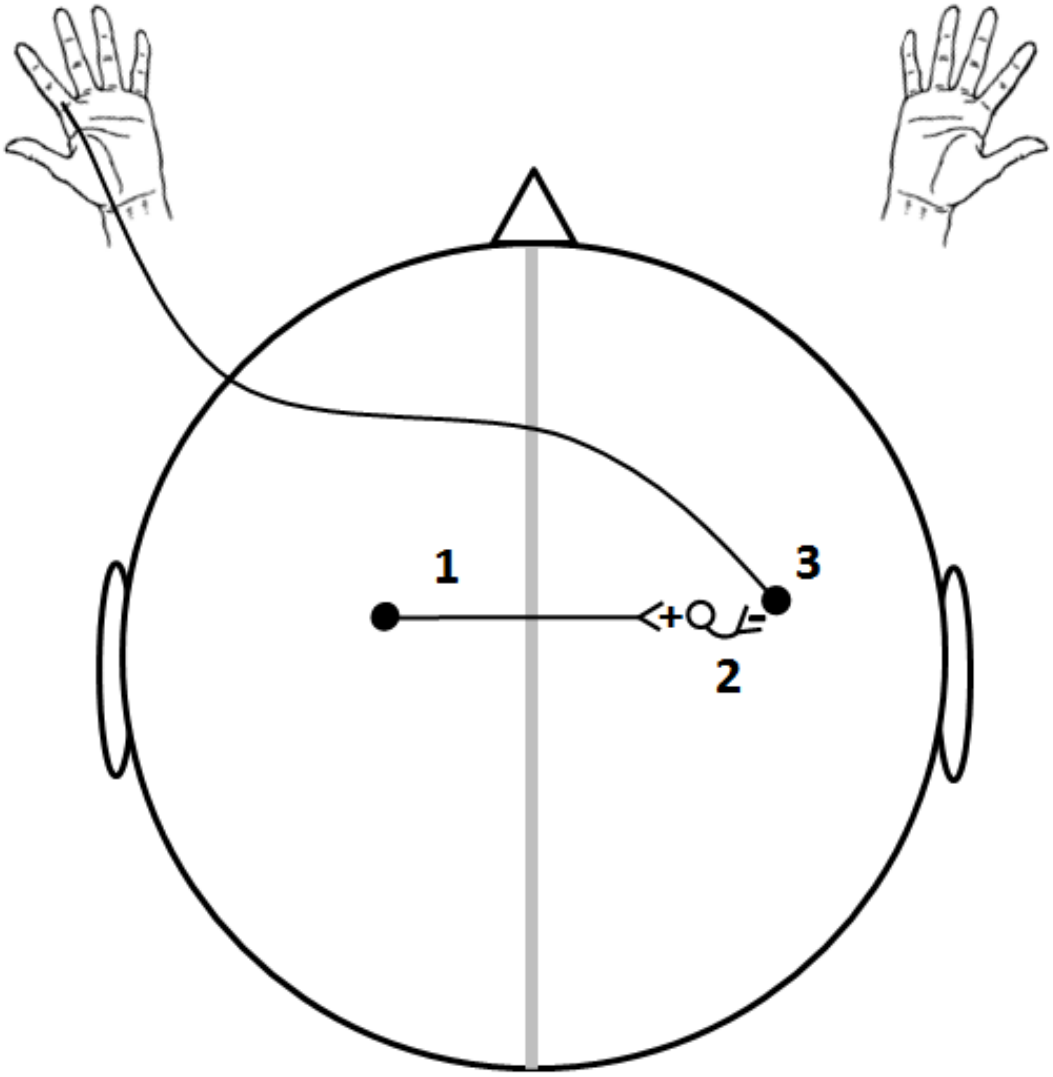

Figure 6.1. Accepted mechanism by which IHI acts to inhibit motor output. Filled circles represent excitatory projections, open circles represent inhibitory projections. Mechanism acts as such:

1. Excitatory transcallosal projections synapse onto inhibitory interneurons in the opposite M1.

2. Inhibitory interneurons activated by transcallosal projections synapse onto corticospinal output circuitry.

3. Corticospinal output circuitry excitability is decreased, resulting in decreased MEP amplitude.

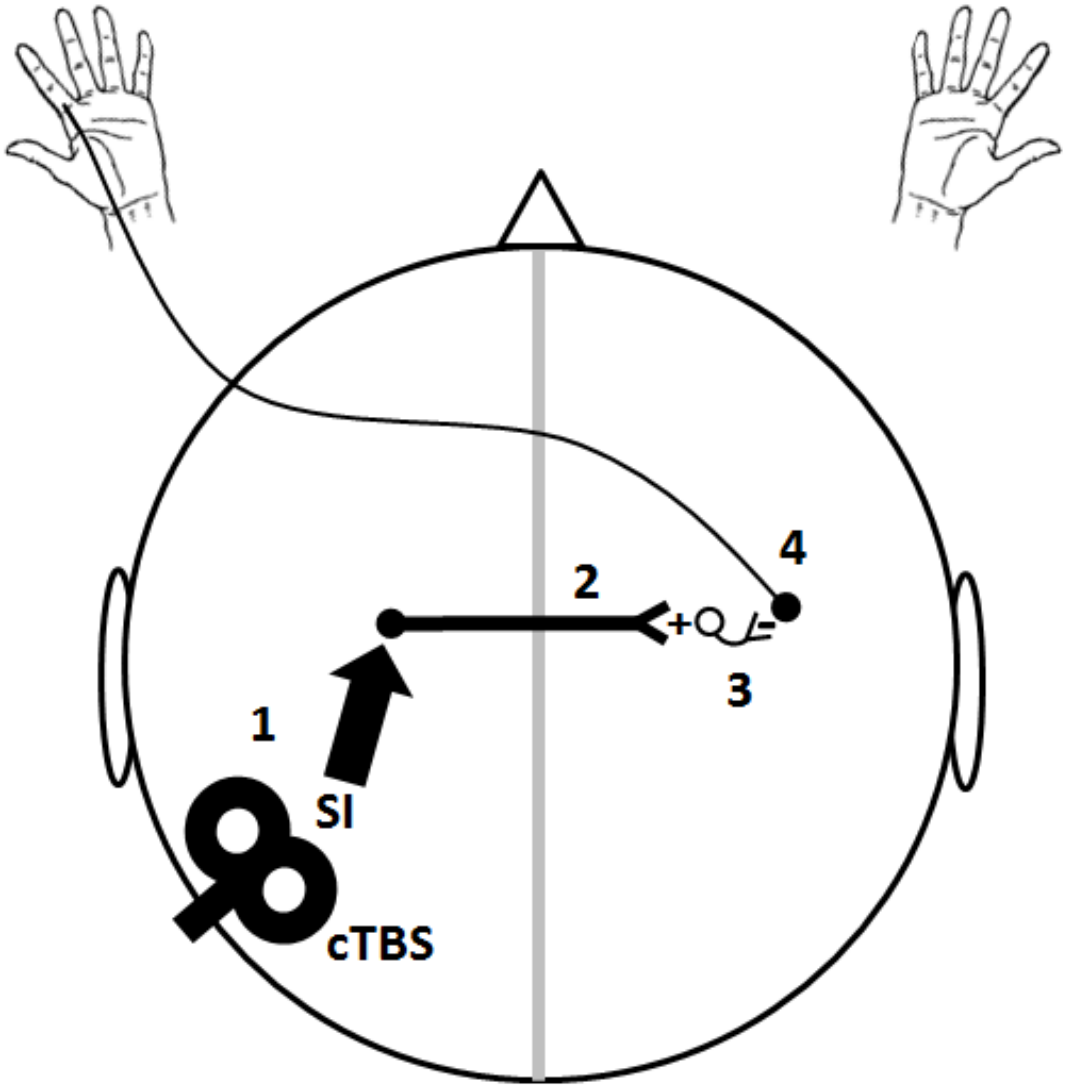

Figure 6.2. Proposed mechanism for the results seen in Experiment 1. Filled circles represent excitatory projections, open circles represent inhibitory projections, arrows represent likely source of action. Proposed mechanism acts as such:

1. CTBS over left SI increases excitability of the transcallosal excitatory projections, either via facilitation of excitatory pathways, or inhibition of inhibitory circuits.

2. Excitability in transcallosal excitatory projections is increased.

3. Inhibitory interneuron activity is increased due to facilitation from transcallosal connections, resulting in increased inhibition of corticospinal output circuitry.

4. Decreased excitability of corticospinal output circuitry results in decreased MEP amplitude.

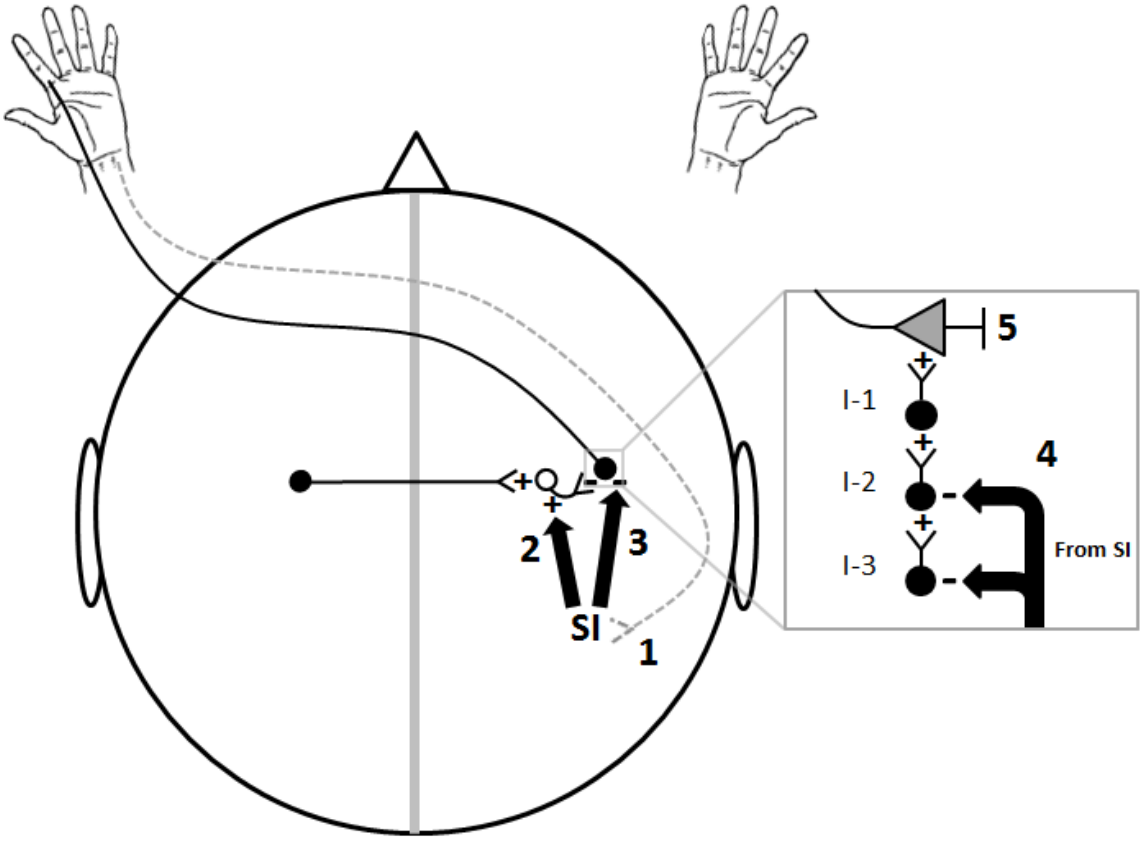

Figure 6.3. Proposed mechanism for the results seen in Experiment 2: inputs applied contralateral to the TS hemisphere. Filled circles represent excitatory projections, open circles represent inhibitory projections, triangle represents corticospinal output neurons, arrows represent likely source of action. Proposed mechanism acts as such:

1. Somatosensory input arrives at SI. Two mechanisms by which SI may alter corticospinal output are depicted.

Mechanism 1:

2. SI may facilitate the inhibitory interneurons responsible for mediating IHI. Increased excitability in these interneurons would result in decreased excitability of corticospinal output circuitry, resulting in decreased MEP amplitude.

Mechanism 2:

3. SI may inhibit I-wave generating circuitry responsible for creating descending motor outputs.

4. Inhibition of I-wave circuitry likely occurs at the I-2 or I-3 level.

5. Decreased corticospinal neuron activity results in decreased MEP amplitude.

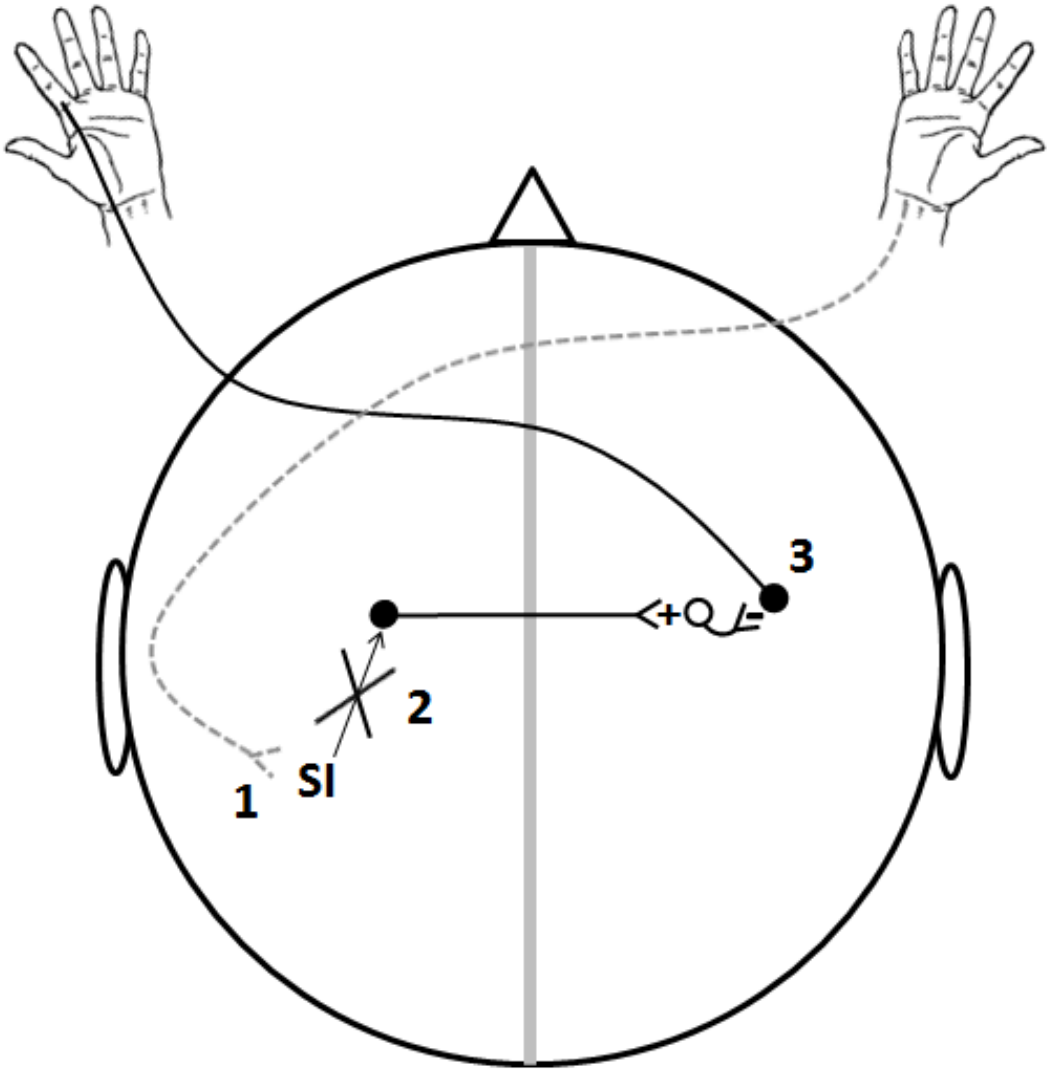

Figure 6.4. Proposed mechanism for the results seen in Experiment 2: inputs applied contralateral to the CS hemisphere. Filled circles represent excitatory projections, open circles represent inhibitory projections, arrow represents predicted site of action. Proposed mechanism acts as such:

1. Somatosensory inputs arrive at SI.

2. SI has no effect on excitatory transcallosal projections.

3. No change in corticospinal output or MEP amplitude is observed.

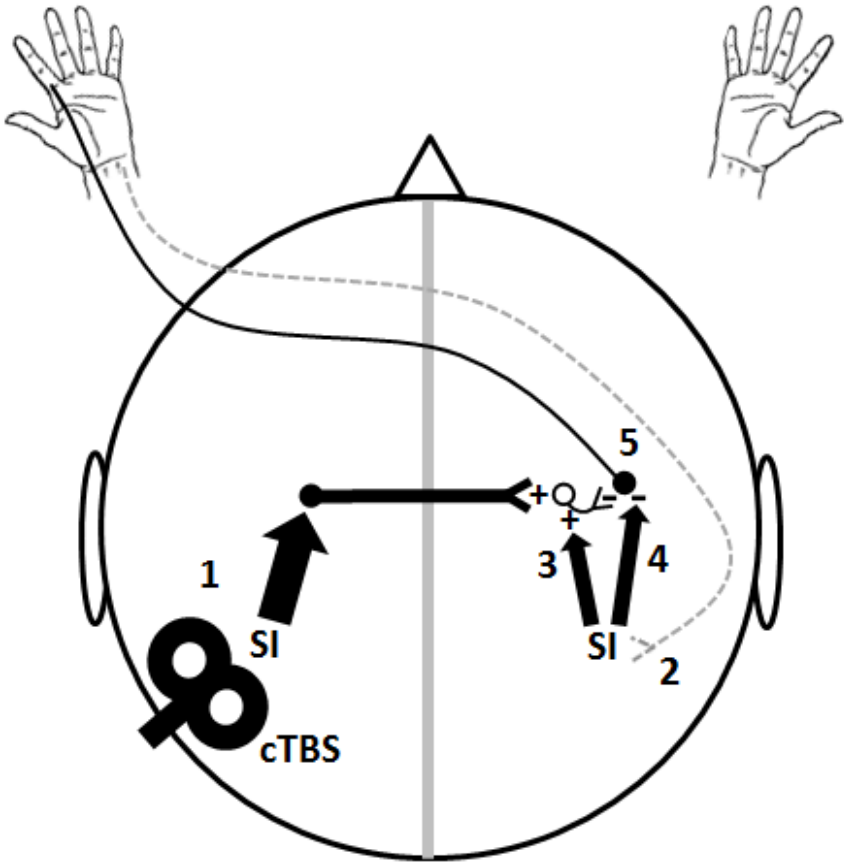

Figure 6.5. Overall proposed mechanism for the experiments conducted in this thesis. Filled circles represent excitatory projections, open circles represent inhibitory projections, triangle represents corticospinal output neurons, arrows represent likely source of action. Proposed mechanisms act as such:

Direct Cortical Stimulation

1. CTBS over left SI excites the transcallosal excitatory projections, resulting in increased excitability of inhibitory interneurons in the opposite hemisphere, and thus decreased corticospinal output resulting in decreased MEP amplitude.

Peripheral somatosensory inputs

2. Somatosensory input arrives at SI. SI may alter corticospinal output in either of 2 ways:

Mechanism 1:

3. SI excites inhibitory interneurons responsible for mediating IHI. This results in decreased excitability of corticospinal output circuitry and thus decreased MEP amplitude.

Mechanism 2:

4. SI inhibits corticospinal circuitry responsible for creating descending motor outputs.

5. Decreased corticospinal activity results in decreased MEP amplitude.

Chapter 7: References

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