CONTINUOUS THETA BURST STIMULATION COMBINED WITH SKILLED MOTOR PRACTICE AFTER STROKE: EFFECTS ON IMPLICIT LEARNING AND ELECTRONEUROPHYSIOLOGY

by

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ABSTRACT

After stroke, cortical excitability is decreased in the ipsilesional primary motor cortex and increased in the contralesional primary motor cortex. This abnormal pattern of excitability detrimentally affects performance with the hemiparetic arm. Short lasting improvements in motor performance occur following repetitive transcranial magnetic stimulation (rTMS) over the contralesional hemisphere after stroke; however, no work has considered the impact of pairing rTMS with skilled motor practice over multiple days on motor learning, hemiparetic arm function, or electroneurophysiology in the brain. The aim of this thesis was to determine the impact of 3 days of continuous theta burst stimulation (cTBS) over contralesional primary motor cortex paired with skilled motor practice on 1) learning of a novel motor task and hemiparetic arm motor function and 2) levels of intracortical inhibition, intracortical facilitation, and transcallosal inhibition following stroke. In a cross-over design, participants with chronic stroke were randomized to first receive either active or sham cTBS over the contralesional primary motor cortex. Functional measures, motor task performance, and electroneurophysiology were assessed at baseline. 3 days of cTBS paired with skilled motor practice were completed; functional measures, motor learning, and electroneurophysiology were re-evaluated at post-testing. After a 2-week washout period participants underwent the second half of the study with the other form of cTBS. Participants showed larger motor learning related change following active cTBS than sham cTBS. The magnitude of this improvement correlated with enhanced performance on standardized measures of arm function after stroke. Active cTBS also decreased levels of facilitation in the contralesional hemisphere and decreased the amount of inhibition being sent from the contralesional hemisphere to the ipsilesional hemisphere. No adverse effects were reported. Results of this thesis suggest that cTBS over the contralesional motor cortex

paired with skilled motor practice facilitates both improved hemiparetic arm function and motor learning beyond that seen with skilled motor practice alone. The results of this thesis contribute to research relevant to rehabilitation of individuals with stroke and may facilitate the development of new rehabilitation strategies to improve functional recovery after stroke.

PREFACE

This thesis contains two experiments that were conducted by the candidate, Meghan A. Linsdell, under the supervision of Dr. Lara Boyd with guidance from Drs. Janice Eng and James Carey. The collection, analysis, and writing of all experiments was principally the work of the candidate. Sections of this thesis will be submitted for publication as multi-authored manuscripts in peer-reviewed journals. Ethical review and approval for this thesis was performed by the UBC Clinical Research Ethics Board (H08-01898).

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LIST OF ABBREVIATIONS

AMT	Active Motor Threshold
ANOVA	Analysis of Variance
BBT	Blocks to Box Test
CS	Conditioning Stimulus
CSI	Conditioning Stimulus Intensity
cTBS	Continuous Theta Burst Stimulation
ECR	Extensor Carpi Radialis
EMG	Electromyography
FHT	Functional Hand Task
FM	Fugl-Meyer Assessment of Motor Recovery After Stroke
fMRI	Functional Magnetic Resonance Imaging
ICF	Intracortical Facilitation
IHI	Interhemispheric Inhibition
ISI	Interstimulus Interval
iTBS	Intermittent Theta Burst Stimulation
JTT	Jebsen Taylor Test of Hand Function
LTD	Long Term Depression
LTP	Long Term Potentiation
M1	Primary Motor Cortex
MCA	Middle Cerebral Artery
MEP	Motor Evoked Potential
MRI	Magnetic Resonance Imaging

MVC	Maximum Voluntary Contraction
ppTMS	Paired Pulse Transcranial Magnetic Stimulation
RMT	Resting Motor Threshold
RT	Response Time
rTMS	Repetitive Transcranial Magnetic Stimulation
SE	Standard Error
SICI	Short Latency Intracortical Inhibition
SRT	Serial Reaction Time
TBS	Theta Burst Stimulation
TCI	Transcallosal Inhibition
TMS	Transcranial Magnetic Stimulation
TS	Test Stimulus
WMFT	Wolf Motor Function Test

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CHAPTER 1: Introduction and purpose

1.1 Introduction

In the developed world, stroke is the third highest cause of death[1] and the leading cause of long-term adult disability[2]. Stroke causes the deaths of approximately 16000 Canadians each year[3]. Most individuals with stroke demonstrate some neurological recovery but 30-60% remain dependent upon others for some activities of daily living[1]. Current stroke rehabilitation techniques focus on the acute period and often encourage the use of the unaffected hand for the performance of activities of daily living. However, this approach may limit rehabilitation outcomes.

After a stroke, the most rapid recovery occurs in the first 30 days[4]. Much of this early improvement is spontaneous in nature and might occur regardless of interventions. This spontaneous recovery is due to a decrease in the swelling of the brain and a structural reorganization of synapses[5]. Following this initial period, recovery slows and eventually plateaus. In the past some assumed that once an individual with stroke reached a plateau in their recovery that therapeutic interventions no longer stimulated substantial improvements in function. However, it is now apparent that the stroke affected brain is capable of neuroplastic change years after the initial event[6, 7].

To augment recovery of function after stroke newer techniques are being formulated. One newer experimental technique uses transcranial magnetic stimulation to either enhance or suppress the activity of a given brain area. By repetitively stimulating at higher frequencies (i.e., >5 Hz) researchers may be able to effectively increase the activity in the lesioned hemisphere to improve use of the hemiparetic limb. In a related fashion, by decreasing activity in the

contralesional hemisphere using lower frequencies of stimulation (i.e., <1 Hz), the ipsilesional hemisphere may be freed from some transcallosal inhibition and allowed to return to a more normal state of excitability. These changes then may translate into improved function. These effects will be discussed in greater detail later in this chapter (see Transcranial Magnetic Stimulation and Interhemispheric Interactions sections).

1.2 What is a Stroke?

There are two main types of strokes, hemorrhagic and ischemic. Hemorrhagic strokes occur when a blood vessel in the brain ruptures causing bleeding and a lack of blood flow to the areas supplied by that vessel. Ischemic strokes occur when a vessel becomes blocked, either by a blood clot that has traveled from elsewhere in the body (embolic stroke) or by a narrowing of the vessel due to plaque build-up (thrombotic stroke)[8]. Immediately after a stroke occurs there is a lack of blood flow to the area of brain supplied by the artery.

Depending on the affected brain area, individuals with stroke will experience different symptoms. The most noticeable symptoms of stroke are weakness, difficulty speaking, blurred vision, dizziness, and sudden headache[3]. One of the most common motor symptoms of stroke is hemiparesis, an inability to control the muscles on the side of the body opposite the side of the stroke. After stroke, 75% of people are left with varying degrees of lasting functional impairments[3]. As time goes on, many individuals will begin to see their symptoms diminish, though quite often the extent to which recovery occurs is determined by the severity of initial impairments[4].

1.3 Plasticity of the Brain

In the past, it was thought that once a person reached adulthood their brain was in a stable state and that no new changes could be made. Thus, if an adult suffered any type of brain injury there was limited chance for them to recover. More recently, it has been shown that there is extensive plasticity within the human nervous system[5, 9]. Plasticity refers to the ability of the nervous system to change in response to injury or experience and can involve neuronal changes in structure, function, or chemical profile[8].

Much of the work that is performed examining cortical adaptation began with research in animal laboratories. A great deal of animal model work shows that the cortex can adapt in response to training of skilled behaviours. Nudo et al.[5] trained squirrel monkeys to pick up small objects requiring skilled movements. After training was complete, they noted an expansion in the cortical area devoted to the digits and a decrease in the area devoted to the forearm muscles as shown through intracortical microstimulation. In contrast to this, when the monkeys were trained on a task involving pronation and supination of the forearm, the area devoted to these muscles expanded and the area for the digits became smaller. This led them to conclude that the motor cortex is capable of plasticity throughout life in response to specific behaviours[5].

Plasticity has also been shown in human participants. Classen et al.[10] measured the EMG response in the thumb to transcranial magnetic stimulation over the contralateral motor cortex in healthy participants. Participants were then asked to contract the thumb in the opposite direction. After 30 minutes of practice, stimulation over the same spot elicited thumb movements in the direction of practice for 15-20 minutes. This short-term cortical plasticity is likely the first step in skill acquisition[10].

1.4 Transcranial Magnetic Stimulation

Transcranial magnetic stimulation (TMS) is one method by which researchers can test the integrity of the brain after stroke. The parameters of TMS can be varied to produce current that flows monophasically, biphasically, in paired pulses, repetitively, and in a theta burst paradigm among others. In monophasic TMS, the lowest activation threshold occurs when the pulse delivered causes current flow in the posterior to anterior direction at a location perpendicular to the central sulcus[11]. The response to the stimulation can then be measured directly as activity within the activated neurons and indirectly as the activation of a motor unit, measured by electromyography (EMG). As the intensity of the initial stimulus increases, so does the response by the neurons and affected motor unit[11]. Single pulse TMS can be used to briefly disrupt activity in a given brain area. When a pulse is applied to the motor cortex between 100ms before and 200ms after the signal to start a movement, but before the movement actually begins, reaction time is delayed[12]. Stronger initial stimuli induce longer delays.

Intra- and Inter-cortical Excitability.

Paired pulse transcranial magnetic stimulation (ppTMS) may be used to assess the functional connections between cortical sites or inhibition / facilitation in the same area. It involves the application of 2 stimuli separated in time by a varying interstimulus interval (ISI). The first pulse (conditioning stimulus) is given between 1 and 15ms before the second pulse (test stimulus). Short latency intracortical inhibition (SICI) occurs at an ISI between 1 and 5ms and intracortical facilitation (ICF) occurs at ISI 6-15ms[11]. In paired pulse the conditioning stimulus hypo-polarizes local neurons. Depending on the time that the test stimulus is delivered there is either an inhibitory or facilitatory effect. SICI is thought to be mediated through GABAa receptors[13] and ICF through NMDA receptors[14]. An additional measure of the levels of

inhibition between the hemispheres is transcallosal inhibition (TCI). TCI is measured by contracting the target muscle in the arm ipsilateral to stimulation. The length of time EMG responses are suppressed for after a single suprathreshold stimulus is then recorded[15]. After stroke the levels of TCI are altered depending on the location of the stroke[16].

Repetitive TMS

Repetitive TMS (rTMS) can be generally classified into two categories, inhibitory and excitatory. Inhibitory stimulation is described at TMS pulses being delivered at a rate of 1 Hz or below. High frequency is generally delivered at rates of 5 Hz or above. rTMS over the motor cortex at 1Hz has been shown to decrease corticospinal excitability whereas rTMS at 5Hz increases excitability[17]. rTMS is usually applied because the effects of application last beyond the application session itself, at approximately a 1:1 ratio, allowing researchers to test the effect of rTMS on training paradigms[18]. However, very high frequency (10-20Hz) rTMS has been shown to produce 'after-discharges' in electrical activity within target muscles after stimulation has ceased, which may be suggestive of epileptic phenomena[19]. Due to the potential danger of causing a seizure, Rossi et al.[20] published guidelines, which dictate safe levels and frequencies of stimulation. In this most recent review of TMS safety, all reported seizures could be attributed to medical factors (e.g., previous history) or current medication intake[20].

A newer application of TMS is theta burst stimulation (TBS), first described in human participants by Huang and Rothwell[21]. TBS involves the delivery of pulses at a high frequency and low intensity to minimize risk of seizure. There are 2 types of TBS, continuous (cTBS) and intermittent (iTBS). cTBS has been shown to be inhibitory in nature and has after-effects that outlast traditional 1 Hz inhibitory stimulation after only 40s (600 pulses) of stimulation[22]. cTBS is delivered by giving 3 pulses at 50Hz every 200ms (5Hz) at 80% active motor threshold

(AMT). iTBS has been shown to be facilitatory and involves placing 8s of rest between 2s bursts of 50Hz pulses. The effects of TBS are thought to occur through changing the efficiency of synaptic interactions[22]. TBS has been used safely in healthy[21, 22] and stroke[23, 24] participants. The effects of TBS have been compared to conventional rTMS in healthy participants[25]. It was found that while both cTBS and rTMS caused inhibition there were no differences in the levels of inhibition caused by each. Given that cTBS can be delivered in 40s versus 20 minutes for rTMS, and that cTBS is delivered at a lower intensity, it is likely that cTBS is the more efficient and comfortable protocol for use in human studies.

1.5 Interhemispheric Interactions of the Motor Cortex

At rest in the healthy brain the motor areas of one hemisphere exert an inhibitory effect on the other hemisphere. These inhibitions occur through excitatory transcallosal fibers from layer III of one motor cortex to inhibitory interneurons in the other[26]. There are also more minor connections through layer I. The function of interhemispheric inhibition (IHI) is to suppress unwanted movements of the opposite hand during unimanual tasks[27]. This inhibition is greatest in the pre-movement period, peaking on average 97ms after the signal to move is given. By the movement onset period, approximately 159ms after the go signal, inhibition from the hemisphere contralateral to the moving hand turns to facilitation[28]. The initial deep inhibition is thought to prevent mirror movements during task performance. These levels of inhibition in the healthy brain can be modified by repetitive transcranial magnetic stimulation (rTMS). Gilio et al.[29] applied 1Hz inhibitory rTMS over the hand area of the left motor cortex of young healthy participants. They found that the level of excitability in the right hemisphere increased and the amount of inhibition the left hemisphere was exerting on the right was decreased. They

concluded that rTMS of one hemisphere leads to changes in the other, by modifying the levels of resting inhibition between the hemispheres.

1.6 Changes in Interhemispheric Interactions after Stroke

After stroke, bilateral motor cortex activation is consistently seen with movement of only the hemiparetic upper extremity. This bilateral activation persists into chronic phase in a large proportion of those who have a stroke[30]. The levels of activation in the contralesional hemisphere are also higher in those with lower function in their hemiparetic hand[31]. This has led researchers to believe that there is a disruption in the normal balance of interhemispheric inhibition. The level of activation of the contralesional hemisphere is often greater than that of the ipsilesional hemisphere. Laterality index is one way to index these activation levels, and is expressed as the magnitude of activation in the contralateral (to the arm being moved) hemisphere minus the ipsilateral hemisphere divided by the contralateral plus ipsilateral[31]. In a healthy brain this will be equal to 1.0 as there should be no activation in the ipsilateral hemisphere. In the stroke affected brain the laterality index is often negative or close to zero, showing near equal activation in the hemisphere ipsilateral to arm movement to that in the contralateral side[31, 32]. It is thought that the inhibition of the ipsilesional hemisphere on the contralesional is disrupted after stroke, causing the contralesional hemisphere to become more active.

A common technique to measure the levels of inhibition between the hemispheres is paired pulse TMS, as first described by Ferbert[33]. This method involves applying a sub-threshold pulse to the motor cortex of one hemisphere and a supra-threshold pulse to the other 10 ms after the first. The first pulse activates cross-callosal excitatory neurons that act upon inhibitory interneurons in the opposite hemisphere. When the second pulse is delivered a smaller

motor evoked potential than if the pulse was given alone will result due to the influence of the inhibitory interneurons.

After stroke, the level of inhibition from the contralesional hemisphere to the ipsilesional hemisphere increases (Figure 1)[34]. Those participants who show higher levels of inhibition also have a greater impairment of their hemiparetic hand suggesting that the more severe the stroke the more the balance of inhibition is disrupted[28].

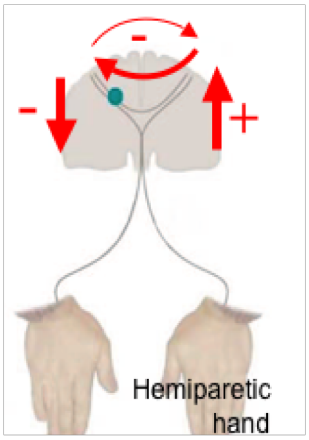


Figure 1: After stroke increased inhibition is placed on the ipsilesional cortex through transcallosal inhibition. The blue disc represents the site of the stroke. Due to decreased activity in the ipsilesional hemisphere there is less functionality in the hemiparetic arm.

Recently, researchers have attempted to change the levels of inhibition between the hemispheres after stroke. A single session of inhibitory rTMS to the contralesional hemisphere in chronic stroke participants was shown to reduce the resting threshold of the ipsilesional hemisphere, making it more excitable[35]. These participants also performed a motor learning task involving modulating pinch force. Those who received the inhibitory rTMS performed better on the task and this improvement in performance lasted through a 1-week follow-up[35]. Fregni et al. [36] examined whether a 5-day course of inhibitory rTMS to the contralesional hemisphere impacted the function of the hemiparetic upper limb. The Jebsen Taylor Test of Hand Function

was measured before rTMS, on day 5, and again at a follow-up 2 weeks later. Resting threshold of the ipsilesional hemisphere was decreased by day 5 and that the amount of change was correlated to improvements in hand function. The improvement in hand function lasted for 2 weeks after testing, showing that rTMS can lead to lasting changes in both cortical excitability and improvements in function of the hemiparetic limb. The intensity of stimulation needed and the dose of both TMS and practice required to produce lasting changes are not known. An essential first step is to combine TMS and task practice to see what the cumulative effects of the combination of the two techniques are.

An open question in the field of repetitive stimulation after stroke centers on the optimal target for brain stimulation. By delivering excitatory stimulation to the ipsilesional hemisphere its excitability can be increased. One problem with this approach is that if the participant has had a cortical stroke in the middle cerebral artery (MCA) region often the motor cortex has been destroyed so there is no primary motor cortex (M1) to stimulate. The alternative approach is to deliver inhibitory stimulation over the contralesional cortex. By inhibiting the contralesional cortex the level of inhibition it exerts on the ipsilesional cortex may be decreased, thus disinhibiting it and potentially allowing it to return to more normal levels of activation (Figure 2). A detriment to much of this work is that the vast majority of studies only examined a single time point[24, 37] and have not employed experimental paradigms that allow measurement of changes in skill acquisition and motor control that may be associated with brain stimulation.

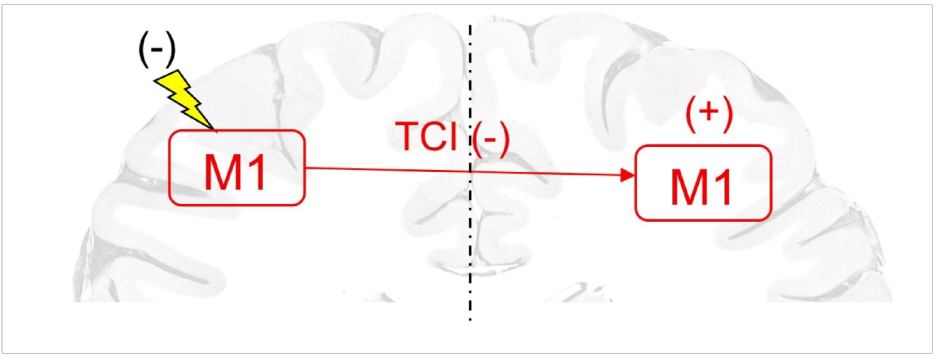


Figure 2: Transcallosal pathway between contralesional M1 and ipsilesional M1. TMS over contralesional M1 reduces transcallosal inhibition and increases cortical excitability in ipsilesional M1.

1.7 Motor Learning

Learning can be divided into 2 categories: implicit and explicit. Explicit learning can be directly assessed and is knowledge for factual information. Implicit learning is not as easy to assess, it is knowledge for performance based items and is usually inferred though changes in performance on a task [38, 39]. Implicit learning occurs without the learner being able to consciously recollect or verbalize what parts of the task they have improved upon.

Thus, the explicit and implicit learning and memory systems differ fundamentally. Explicit knowledge is represented as memory for facts, events, and episodes and may be formed very quickly (even in following 1 exposure to explicit information). It is directly accessible to conscious recollection[40] and is used to guide high-level cognition when decisions are based on complex rules and information.

Conversely, the implicit system's functions are distributed and supportive of multiple behaviors. These include associative learning and non-associative learning, priming, and sequence learning [40]. Implicit motor learning is the ability to acquire a new skill through physical practice without being able to explain what elements of task performance have

improved. The most widely used example of implicit learning is learning to ride a bicycle. Fewer falls let the person know that they have improved at the task, yet they are not able to explicitly state what they are doing to avoid falling[39].

Throughout the lifespan humans are constantly learning new motor skills and adapting these skills to the context at hand. After stroke, the ability to learn new tasks is not abolished[6, 39, 41-43], but the way in which a person affected by stroke learns may be different than that of a neurologically healthy participant[44-46]. A common experimental motor learning task to assess implicit learning is the serial reaction time (SRT) task, first described by Nissen and Bullemer[38]. In the SRT task participants are required to respond to stimuli by pressing a key on a keyboard as fast as possible. The sequence of required responses repeats in a predetermined order, unbeknownst to the participant. With practice, participants perform better on the task, as evidenced by a decrease in response time for the repeated sequence as compared to randomly presented trials, without being aware of their improvement in performance[38, 41].

Various adaptations to the SRT task have been made, including that of Boyd et al[41]. Researchers tested those with moderate and severe stroke, as well as aged matched controls, on a functional version of the SRT task that involved pushing elevator buttons and turning keys following a repeated sequence. This was then compared to performance on the classic key-press SRT task. All groups showed greater change on the functional version of the serial reaction time task where objects of daily life were used for responses. However, participants with severe stroke did not improve to the same extent as the healthy controls. In addition, the control and mild stroke group showed more change on the functional task than on the classic SRT task. The authors concluded that though all individuals were able to learn, those with severe stroke had a decreased overall capacity for implicit learning[41].

The primary purpose of this thesis was to investigate the effects of transcranial magnetic stimulation induced inhibition of the physiologically active unaffected, contralesional primary motor cortex after stroke. The experiment was divided into 2 papers to address our specific aims. We hypothesized that inhibition of contralesional primary motor cortex would decrease the level of transcallosal inhibition exerted on the affected, motor homolog in the stroke lesioned hemisphere. We expected that by inhibiting the contralesional hemisphere, the ipsilesional hemisphere would be more easily excited by voluntary movement and this in turn would facilitate motor skill learning.

1.8 Specific Aims

Specific Aim 1: To determine whether repetitive inhibitory cortical stimulation of the contralesional primary motor cortex facilitated learning of a sequential motor learning task that employed functionally based movements in individuals with chronic stroke. Chapter 2 reports the results for this aim.

Repetitive inhibitory stimulation over contralesional motor cortex alters transcallosal inhibition and in turn, facilitates learning of a serial functional hand task consisting of repeated, ordered movements (e.g., push elevator button, turn door handle, slide lock, press light switch).

Hypothesis 1: I hypothesized that individuals who received repetitive inhibitory stimulation to contralesional primary motor cortex would show greater change between random and repeated sequences at retention as compared to individuals who received sham stimulation. This would be demonstrated at a retention test by increased speed (faster response times) during repeated sequence task performance.

Specific Aim 2: To study changes in intracortical inhibition before and after repetitive cortical inhibitory stimulation. Chapter 3 reports the results for this aim.

After stroke, the contralesional hemisphere exerts inhibition over the lesioned hemisphere. It is currently not known what purpose this inhibition serves, whether it is epiphenomenal and has no effects, or whether it hinders function of the lesioned hemisphere.

Hypothesis 2: I hypothesized that repetitive inhibitory stimulation would cause a decrease in the inhibition exerted on the lesioned hemisphere by the contralesional hemisphere as evidenced by a change from pre to post training in the threshold for intracortical inhibition measured by paired pulse transcranial magnetic stimulation over the ipsilesional hemisphere.

Hypothesis 3: I hypothesized that the level of inhibition exerted on the ipsilesional hemisphere by the contralesional hemisphere would decease after repetitive inhibitory stimulation of the contralesional hemisphere as evidenced by a shorter ipsilateral silent period measured by transcallosal inhibition.

CHAPTER 2: Continuous theta burst stimulation over the contralesional motor cortex combined with skilled motor practice: a multi-day, cross-over trial

2.1 Introduction

Approximately 55%-75% of individuals with stroke suffer from chronic impairments in arm function[47]. After stroke, cortical excitability is decreased in the ipsilesional and increased in the contralesional primary motor cortices (M1)[48]. Combined, these changes hamper hemiparetic arm use and impede functional recovery. Increasing hemiparetic arm use elevates the excitability of the ipsilesional cortex[31] and improves function[49]. One method that may be effective in changing cortical excitability is repetitive transcranial magnetic stimulation (rTMS).

Repetitive TMS is a noninvasive method of brain stimulation. In humans, rTMS applied at high frequencies (>5Hz) can increase cortical excitability; conversely, at low frequencies (<1Hz) it can decrease cortical excitability[50-52]. While rTMS in isolation can change cortical excitability after stroke[53] its impact on neuroplastic change is small, likely reflecting a lack of consolidation in the absence of paired motor behavior[31, 53]. Modulating the activity in a given neural network with rTMS prior to motor skill practice may in essence prime the system and enhance the neuroplastic effects associated with learning new motor skills. To date, few studies have paired rTMS with repeated bouts of practice of a novel motor task and assessed changes in motor function or behavior. By decreasing excitability in the contralesional hemisphere or increasing excitability in the ipsilesional hemisphere or both, function in the hemiparetic arm may be enhanced.

Intuitively, it seems simplest to employ high frequency rTMS over the ipsilesional cortex to enhance cortical excitability. However, because of the difficulty of locating stimulation targets in the damaged hemisphere due to structural damage caused by the stroke, low-frequency rTMS

applied over the contralesional cortex may be the better approach[31, 54, 55]. Though the direct effect of low-frequency rTMS in the human cortex is to suppress activity in the stimulated region[31, 36, 47, 54] it also indirectly influences excitability in other areas of the brain[56, 57]. For example, low-frequency rTMS over M1 increases cortical activity in the contralateral M1 homologue[29].

A newer variant of rTMS, continuous theta burst stimulation (cTBS) was recently developed and proposed as a more effective and longer lasting way of inhibiting the cortex[22]. cTBS has been shown to be safe in the stroke population[23, 58]; however, to date no investigations have considered the effect of repeated bouts of cTBS paired with skilled motor practice on either motor learning or hemiparetic arm function.

The purpose of the present study was to test whether using cTBS to suppress the contralesional M1 would facilitate a neural environment that is conducive to neuroplastic change. It was predicted that pairing inhibitory brain stimulation over the contralesional cortex with skilled motor practice over multiple days would enhance hemiparetic arm function and learning of a novel motor task. To date no work has examined pairing of TBS with skilled movement practice over multiple sessions.

2.2 Methods

A cross-over design was employed whereby participants completed 2, 5-session treatment arms; each contained a different form of stimulation, active cTBS or sham cTBS. A washout period of 20.4 ± 6.9 days separated treatment arms[24, 36]. Figure 3 contains an overview of testing procedures.

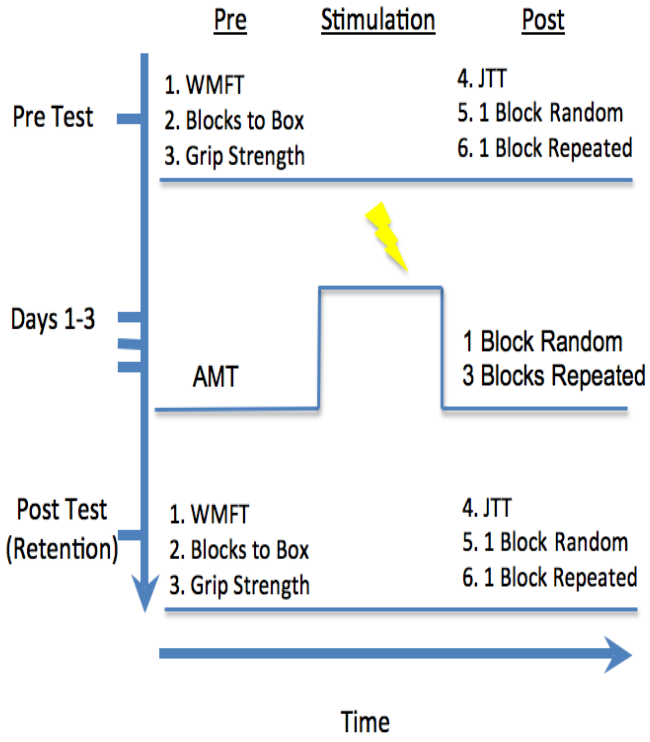


Figure 3: Testing procedure for each arm of the cross-over.

Participants

7 individuals aged 66 ± 8.24 years, with a single, chronic stroke (mean time post stroke 7.28 ± 6.23 years) were recruited from the local community (Table 1). Participants were free from contraindications to TMS including metal in the head, seizure history, or neurological disorder other than stroke. Each participant underwent anatomical MRI scanning to identify lesion location and for use with TMS stereotaxic registration.

Table 1: Participant demographics

Participant No.	Age	Gender	Time Poststroke*	Fugl-Meyer	Lesion Location
01	59	M	3	66	R Pons
02	67	M	5	51	R Basal Ganglia
04	65	M	5	63	R Basal Ganglia
07	58	M	20	50	L MCA territory
08	64	M	4	59	R Insular cortex
09	83	M	3	54	R Insular cortex
10	66	F	11	63	R Insular cortex
Mean	66		7.28	58	
SD	8.24		6.23	6.38	

* In years, Fugl-Meyer upper extremity portion only (maximum = 66), MCA = middle cerebral artery

Functional Testing

The Jebsen-Taylor Hand Function Test (JTT) and a sub-set of hand items from the Wolf Motor Function Test (WMFT; pick up can, pick up paper clip, fold towel) indexed hand function. Grip strength was tested using a Jamar Hand Dynamometer (Sammons Preston, Illinois). The Blocks to Box test (BBT) was performed to index changes in motor performance. The JTT, WMFT, and BBT all have good reliability and validity in people with stroke[59-61]. These tests occurred on the first and last day of testing of each arm of the cross-over. All measures were completed for both the hemiparetic and non-hemiparetic limbs.

Transcranial Magnetic Stimulation

An anatomical MRI from each participant was obtained from participation in previous research in the Brain Behaviour Lab and used with a Brainsight (Rogue Research, Montreal) system for stereotaxic registration of the participant to guide coil placement. The extensor carpi radialis muscle (ECR) was chosen as the stimulation site for 2 reasons. First, in participants with stroke it is often not possible to activate intrinsic hand muscles with TMS. Second, the tasks that were performed involved the use of the wrist extensor muscles. Resting (RMT) and active motor threshold (AMT) were measured by single pulse TMS (Magstim Rapid^2, Magstim, Wales) and

electromyography (EMG) (PowerLab, AD Instruments, Colorado Springs). RMT was defined as the minimum level of stimulator output necessary to evoke a motor evoked potential (MEP) of >50μV in 5 of 10 trials in the ECR with the coil positioned tangentially to the scalp and the handle pointed backward at approximately 45^{o} to the sagittal plane. Active motor threshold (AMT) was measured as the lowest stimulator intensity to evoke a response of >200μV in 5 of 10 trials while maintaining a voluntary contraction 20% of maximum.

Continuous Theta Burst Stimulation

Participants were assigned to receive either active or sham continuous theta burst stimulation (cTBS). Stimulation was delivered via an active, air-cooled 70 mm figure of eight coil or a custom sham coil that is identical in appearance and sound to the active coil. Participants were counter balanced to receive the first stimulation type, and were then crossed over to receive the opposite type of stimulation in the second half of the study. 600 pulses were delivered at 80% AMT over the previously determined target for ECR in the contralesional hemisphere. During theta burst stimulation 3 pulses were presented at 50Hz every 200ms for a total of 40sec[22]. All participants were naive to TMS and were not explicitly informed of the sham condition.

Behavioural Task and Testing

Immediately following cTBS, all participants practiced a novel serial reaction time task that required the performance of four functional hand movements: the functional hand task (FHT). Participants were seated in front of a table with one of two functional hand task boxes (Figure 4) placed on the table at 60% of their arm length to ensure equal effort across participants. The items on the FHT box #1 consisted of (from left to right) a standard elevator push button, a lever-style door handle pointing right, a dead bolt, and a rocker light switch. On

the FHT box #2 there was a rotated door handle (pointing left), a button, a horizontal switch, and a gate latch. A custom computer software program (Presentation platform, Neurobehavioral Systems, Inc, Albany, CA) presented a picture on a 17" computer screen of the functional item. The screen was placed 22cm behind the box. The appearance of a picture of one of the objects signaled the participant to respond by completing the functional task (e.g. push the elevator button). Once the device was manipulated or 3 seconds passed, there was a variable wait time (250ms to 1000ms) and the next cue to move was shown. The movements either followed a repeating 12-element sequence or a random presentation order. All responses were made with the hemiparetic arm. Participants were required to complete 3 blocks of a 12-element sequence and 1, 12-element block of random practice on each training day. The sequence was repeated ten times within a block resulting in 120 trials or individual responses. The end of one block and the beginning of the next were not marked. Participants were not informed of the presence of the repeating sequence. Response time (reaction time + movement time; RT) of each movement was stored for later analysis. Participants were counter balanced to receive FHT box 1 or box 2 in the first portion of the study; the other FHT box was then used for the second part of the cross-over. The FHT has been found to be a reliable tool ($r^2 = 0.87$)(Linsdell et al, unpublished observations).

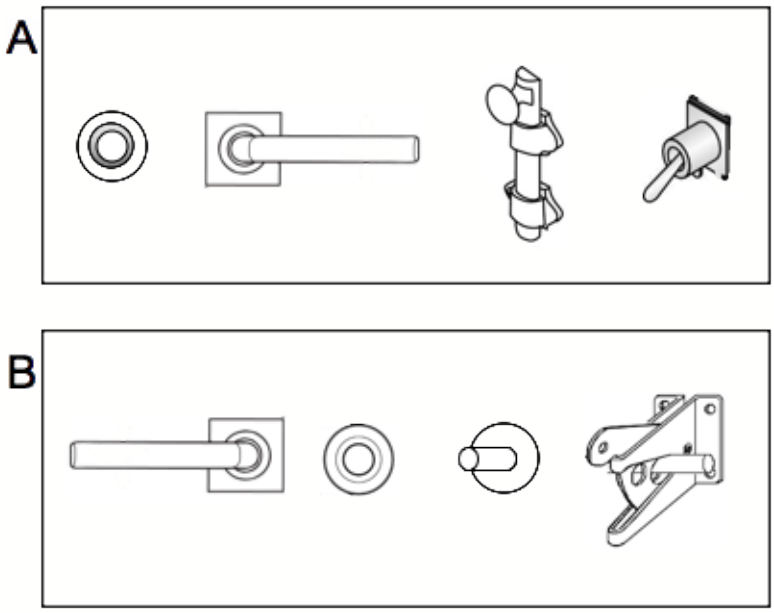


Figure 4: The functional hand task. Participants were randomized to practice on box 1 (A) or box 2 (B) first. Following a 2-week wash-out period they practiced on the other box. The repeated sequence for box 1 was 2-1-3-2-4-1-3-4-2-3-1-4, devices numbered 1-4, left to right. For box 2 it was 4-1-3-2-4-3-1-4-2-3-1-2.

On testing Day 5 no-TMS retention and explicit knowledge tests were performed. The retention test consisted of 1 block of the repeated sequence and 1 block of random sequence on the FHT; the order of random and repeated blocks on day 5 was counterbalanced across participants. Explicit knowledge assessment was performed in 3 steps[39]. Subjective explicit knowledge was tested by verbally asking if the participant noticed anything about the task over the training days. Recognition memory was tested by using the computer screen to visually show 3 different sequences of items; at the conclusion of each the participant was asked to declare if they recognized it as one they practiced during their training session. 1 of the blocks shown was 'true' (i.e. it was the repeated sequence), while 2 blocks were 'foils' and had not been previously shown. Recall memory was assessed by playing a series of 3 items from the repeating sequence and asking what should come next in the series; 3 repetitions were completed.

After participants had completed the first testing phase of the cross-over, a minimum two-week washout period occurred[24, 36]. Participants then returned for the second part of the cross-over, where they received the opposite type of stimulation. Additionally, the other FHT box was employed and new repeating and random sequences were practiced. All other testing procedures were identical to the first half of the experiment.

Participants were also instructed to wear accelerometers for 3 days before testing began, and for 3 days after each arm of the cross-over. Accelerometers (Phillips Respironics, Andover, MA) were worn on both wrists and the hip to measure the number of movements made with each arm and to examine whether stimulation resulted in increased or decreased arm use outside of the lab.

Statistical Analysis

Statistical analyses were performed with SPSS statistical software (version 18). For performance on the FHT, the mean of the median RT for each block was calculated separately for the random and repeated sequence. The impact of practice on repeated and random sequence learning was considered with a Stimulation (active, sham cTBS) by Time (pre-test, days 1, 2, 3) Repeated Measures ANOVA with median RT as the dependent measure. To consider the impact of cTBS separately on motor learning versus motor control this analysis was run with RT from random sequence and repeated sequence as the dependent measure. To evaluate the impact of cTBS on skill learning we conducted a Stimulation (active, sham cTBS) by Sequence (repeated, random) ANOVA with a repeated measures correction using data from the no-cTBS retention test.

To assess the impact of brain stimulation on hemiparetic arm function a Time (pre, post) by Stimulation condition (active, sham) Repeated Measures ANOVA was performed separately

with each functional task (BBT, grip strength, WMFT) for both the hemiparetic and non hemiparetic-arm as the dependent measures.

To test if changes in functional measures correlated with performance on the FHT Pearson correlation coefficients were calculated.

Additionally, the total number of arm movements over the 3-day period following testing was calculated. A Time (Pre, Post) by Stimulation condition (active, sham) Repeated Measures ANOVA was performed to assess changes in arm use.

2.3 Results

All participants tolerated repeated bouts of cTBS without reports of any major adverse effects (seizure, headache, hearing problems, nausea, mood changes). Participants were unable to differentiate between active and sham stimulation based on self-report.

Functional Hand Task

Task practice benefited both conditions as shown by a main effect of Time ($F(9, 45)=22.695$, $p=0.003$), which revealed that both groups shortened response time for the repeated sequences following 3 days of task practice. Consistent with past literature[6, 41] a similar result was evident for random sequence practice (main effect of Time; $F(9, 45)=7.777$, $p=0.032$). There was no Stimulation by Time interaction ($F(9, 45)=3.534$, $p=0.109$) (Figure 5).

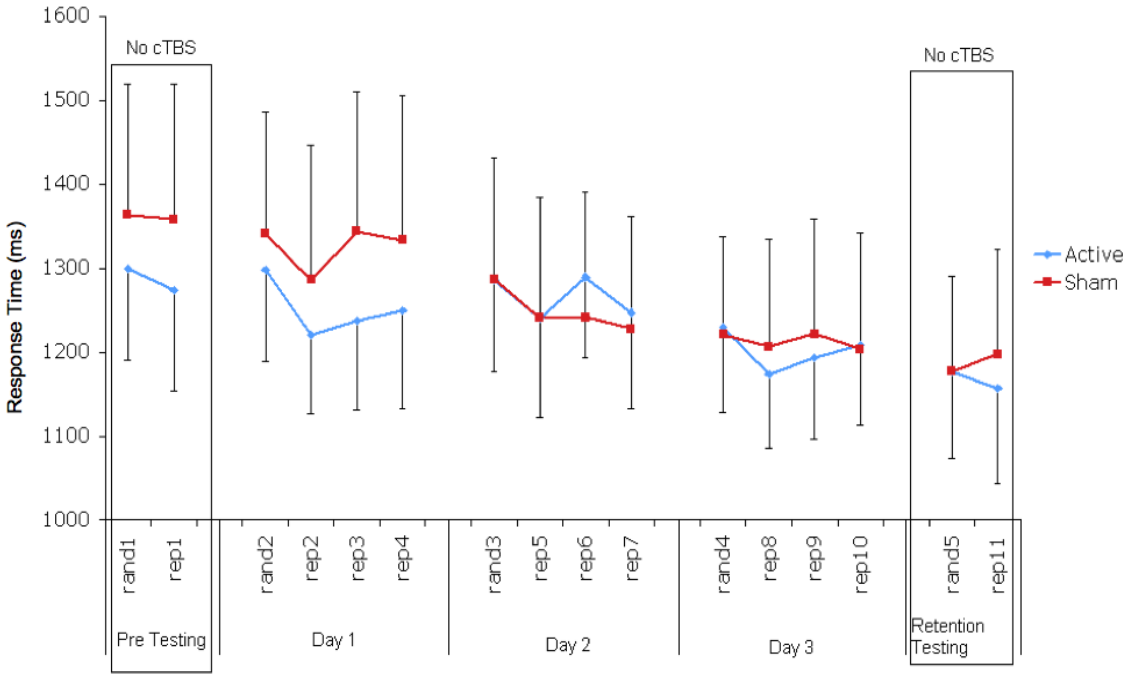


Figure 5: Performance on the FHT. Data are shown as median response time with SE bars. Practice after both active and sham stimulation significantly reduced response time.

At retention testing performance on the FHT was assessed in the absence of cTBS. We discovered an interaction effect of Stimulation and Sequence ($F(1,6)=6.932$, $p=0.039$) showing that active cTBS stimulation paired with skilled motor practice facilitated learning of the repeated sequence of movements (Figure 6). There was a moderate effect size for the change between the random and repeated sequence after active and sham stimulation (Cohen's d=0.66)

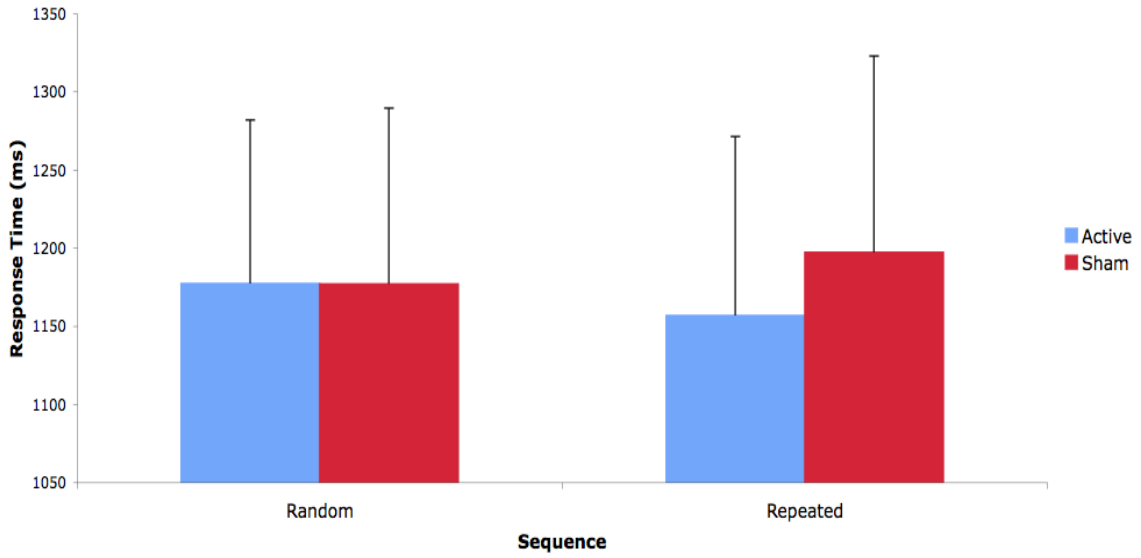


Figure 6: Retention testing of the FHT. Data are shown as median response time with SE bars. There were no differences for the random sequence after active or sham stimulation. After active stimulation, participants responded significantly faster on the repeated sequence.

Explicit knowledge of the repeating sequence was assessed on day 5 of each arm of the cross-over. After both active and sham contralesional cTBS, 1 of the 7 participants was able to subjectively identify that there was a repeating sequence. No participants demonstrated recognition or recall memory for the repeated sequence.

Functional Measures

For the hemiparetic arm, the BBT showed a significant Stimulation condition by Time interaction ($F(1,6)=31.426$, $p=0.001$). Importantly, cTBS over the contralesional hemisphere did not impact the non-hemiparetic arm as none of our measures for this arm changed pre to post-testing.

JTT data were not normally distributed and were accordingly log transformed. Given the broad variation in the items in the JTT we analyzed performance of its 7 component items individually. We discovered that there was a significant difference from pre to post for writing ($t(6)=2.488$ $p=0.047$) and feeding ($t(6)=2.448$, $p=0.050$) after active, but not after sham, cTBS.

After active stimulation there was a strong correlation[62] between the change score from pre to post stimulation for the repeated sequence of the FHT and the BBT at the retention test (r=-0.685). This correlation was not present after sham stimulation (r=-0.150) (Figure 7). There were no correlations between the JTT, the WMFT, or Grip strength with FHT performance.

No differences were seen after either active or sham stimulation in accelerometer use for either the hemiparetic or non-hemiparetic arm (p>0.05).

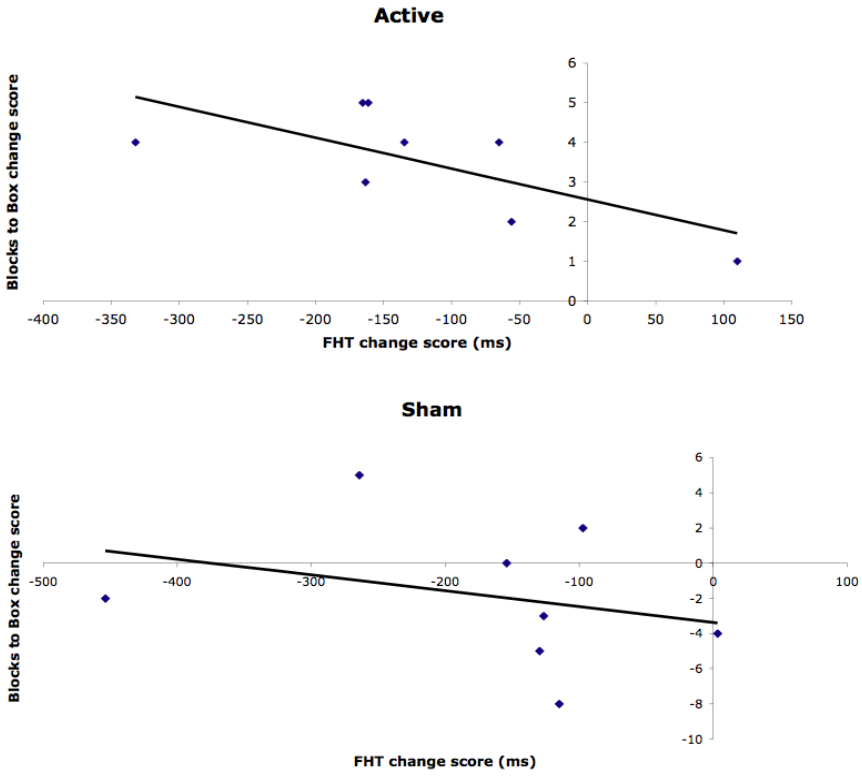


Figure 7: Correlation scores. After active stimulation the change score for the Blocks to Box test was strongly correlated with the change score on the repeated sequence of the FHT. There was no correlation after sham stimulation.

2.4 Discussion

To our knowledge this is the first study to pair multiple days of cTBS with skilled motor practice and to assess the combined effects on motor learning and hemiparetic arm function at a no-TMS retention test. To date, the majority of rTMS studies have consisted of single time point investigations[23, 63], delivered TMS over multiple days without pairing stimulation and skilled motor practice[36], or have failed to consider the residual effects of rTMS plus skilled motor practice at a delayed retention test[24]. We discovered that active cTBS paired with skilled motor practice not only facilitated motor learning but also affected measures of arm function.

Importantly, we discovered that active cTBS paired with skilled motor practice facilitated sequence specific motor learning. This was revealed by significantly reduced response times for the repeated sequence after active cTBS paired with skilled motor practice as compared to sham cTBS. Previous cTBS studies in stroke[24, 37] have failed to show improved performance in the hemiparetic limb after contralesional cTBS. Neither of these studies employed a delayed no-cTBS retention test, nor did they include multiple days of practice or examine sequence specific learning. Previous literature suggests that motor consolidation requires time and is not always immediately evident[64, 65]. Given this, it is possible that had past studies employed a delayed retention test improvements in performance may have been evident. It is also important to consider the number of repetitions performed in each of these studies. A single day of practice is not likely to lead to lasting improvements in behaviour. By performing the task over multiple days, the current study demonstrated the effects of increased task practice. Our results are also consistent with others who have noted that M1 function supports task-specific motor learning rather than global improvements in motor control[66, 67].

Further, we demonstrated significant improvements in the BBT following cTBS paired with skilled motor practice; other work has shown that performance on the BBT correlates with functional independence measures[60]. This suggests that cTBS over contralesional M1 paired with practice may indeed improve the ability of participants to perform activities of daily living using their hemiparetic arm. In addition, the impact of cTBS over contralesional M1 paired with motor practice transferred to benefit writing and feeding elements of the JTT. These transfer effects may be related to the discrete nature of our experimental motor learning task; the FHT requires a precise end point motion, as do writing and feeding items in the JTT. Correlations were only present after active cTBS, but not sham stimulation, over contralesional M1 suggesting that brain stimulation generates a greater capability for neuroplastic change. Task specific training has also been shown to induce more neuroplastic change in M1 as compared to increasing non-specific use of the hemiparetic arm[68]. Furthermore, practice of meaningful tasks appears to stimulate increased transfer of motor skills to functional measures (for a review see Bayona et al[69]). We purposefully designed the FHT to include highly functional items that participants would encounter in every day life to make the tasks more relevant and meaningful to the participants.

It must be noted that cTBS over the contralesional motor cortex is one of several approaches that are being considered to alter cortical activity and stimulate neuroplastic change. Carey et al (2010)[70] noted that primed inhibition over contralesional M1 altered ipsilesional cortical excitability but did not impact performance of the blocks to box test. Facilitatory stimulation of the ipsilesional hemisphere has also been investigated[23] and shown to be effective in disinhibiting the ipsilesional cortex. However, stimulation of the ipsilesional cortex is complicated by difficulty finding targets when the cortex is damaged by stroke. There may also

be a danger of the stimulation 'shunting' along the scar tissue generated by the stroke and affecting unknown distant areas[71].

A key finding from the present study was the absence of negative effects on performance of the non-hemiparetic arm following inhibitory stimulation over the contralesional cortex. It has been suggested that inhibiting the contralesional hemisphere may in fact impair performance by decreasing activity in ipsilateral descending connections to the hemiparetic arm as well as in the contralateral connections to the non-hemiparetic arm[72]. By examining both arms before and after multiple days of stimulation we were able to test for any detrimental effects of stimulation on arm use.

In sum, we found that active cTBS over contralesional M1, when combined with skilled motor practice facilitated sequence-specific implicit motor learning and affected functional measures of the hemiparetic limb after stroke. Importantly these effects were only obvious at a no-rTMS retention test after consolidation of the newly learned motor skills occurred. Our data suggest that it may be possible to combine cTBS over the contralesional M1 with therapeutic interventions that stress functional motor skills. Future studies should examine the viability of combing the brain stimulation with skilled rehabilitation and gage their combined impact on recovery of hemiparetic arm function.

2.5 Bridging Summary

Chapter 2 found that inhibitory cTBS over the contralesional hemisphere facilitated sequence specific motor learning of a novel motor learning task. Additionally, this improvement was associated with functional gains on standardized measures after stroke. It is important to understand the mechanisms underpinning the cause of these improvements. The next chapter will examine how cortical excitability was altered by a 3-day intervention of cTBS plus task practice. Short interval intracortical inhibition, intracortical facilitation, and transcallosal inhibition were measured at pre testing and retention testing to assess how skilled motor practice plus brain stimulation impacted cortical electroneurophysiology in both the ipsilesional and contralesional hemispheres.

CHAPTER 3: Influence of 3 days of continuous theta burst stimulation over motor cortex combined with skilled motor practice on cortical excitability

3.1 Introduction

In the healthy brain at rest normally the two hemispheres mutually inhibit one another[27]. After stroke, however, the level of inhibition placed on the ipsilesional hemisphere by the contralesional hemisphere is increased[28, 34]. As a result there is a decrease in inhibition being reciprocally placed back onto the contralesional hemisphere[16, 73, 74] (see Figure 1 in Chapter 1). These changes in cortical excitability potentially contribute to lasting functional impairments following stroke. The degree of inhibition from the contralesional hemisphere on the lesioned hemisphere is correlated with the level of function in the hemiparetic arm[73, 74]. Additionally, when a laterality index is derived from functional MRI in primary motor cortex it is lower in those participants with lower functional capacity indicating increased activity in the contralesional hemisphere[31, 32]. The laterality index is a measure of the relative contribution of each hemisphere to movements of the hemiparetic limb.

Repetitive transcranial magnetic stimulation (rTMS) has been used to alter short interval intracortical inhibition (SICI) and intracortical facilitation (ICF) in healthy participants. When inhibitory 1Hz rTMS is delivered to the left hemisphere a reduction in IHI from the left hemisphere to the right hemisphere occurs; there is also an increase in the size of MEPs in the right hemisphere[29]. Plewnia et al[75] also showed a decrease in the size of motor evoked potentials (MEPs) after inhibitory rTMS on the stimulated side and importantly a reduction of SICI of the unstimulated hemisphere. rTMS has also been used to alter SICI and ICF after stroke. Carey et al.[70] used 6Hz primed inhibitory 1Hz rTMS in a participant with right middle cerebral artery stroke. After 5 days of stimulation the participant showed a decrease in SICI and an increase in

ICF in the ipsilesional hemisphere. Fregni et al.[36] also tested the effects of 5 days of 1Hz over the contralesional hemisphere in a group of stroke participants. They showed an increase in MEP amplitude from the ipsilesional hemisphere after active but not sham stimulation. The authors concluded that this increase in excitability was due to a decrease in inhibition from the contralesional hemisphere, though this was not explicitly tested.

One method that may be used to index motor cortical excitability is paired pulse TMS (ppTMS). ppTMS was first described by Ferbert[33] and involves the delivery of 2 pulses, a subthreshold conditioning stimulus (CS) followed by a suprathreshold test stimulus (TS). Varying the interstimulus interval (ISI) allows determination of levels of SICI and ICF. ISIs of 1-6ms have been shown to inhibit the resultant motor evoked potential (MEP) while ISIs of 6-15ms facilitate MEPs[76] (Figure 8). The traditional method of ppTMS holds stimulating intensities constant and varies interstimulus intervals across a range from 1-15 ms. This traditional approach to ppTMS relies on resting motor threshold (RMT) in motor cortex to determine the stimulating intensities[77, 78]. However, recent work has shown that the determination of RMT is less reliable than establishing active motor threshold (AMT)[79]. Further, the traditional method of estimating SICI and ICF yields a curve of data rather than a specific threshold for inhibition and facilitation. To account for these two issues, Orth et al. developed a new method for ppTMS[79]. The Orth protocol involves testing varying intensities of the CS to generate recruitment curves for SICI and ICF. The point at which the recruitment curve deviates from zero indicates a specific threshold for SICI or ICF. Importantly, in the Orth protocol CS intensities are based on AMT. When tested in healthy control participants, this method of stimulation has been shown to be more reliable than the traditional paired pulse method[79].

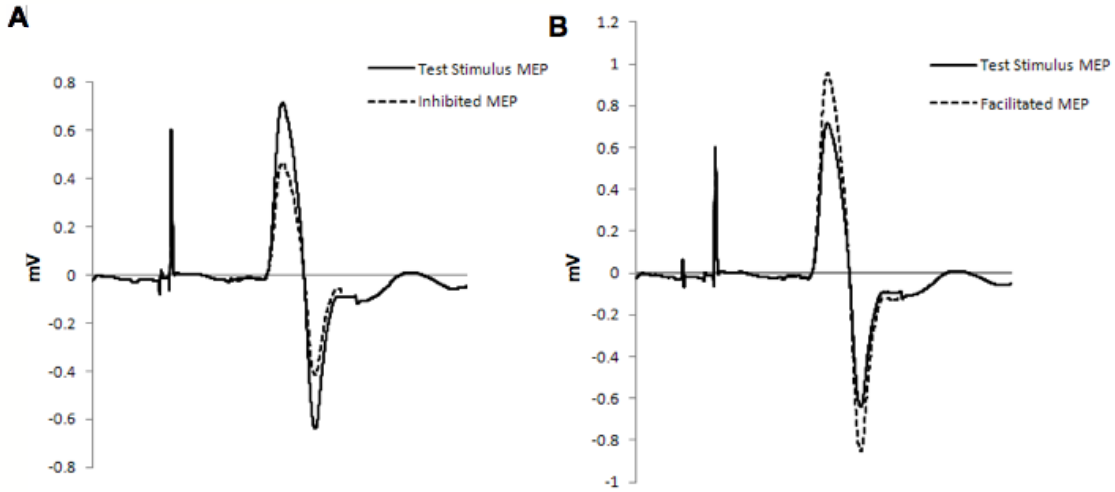


Figure 8: Sample paired pulse MEPs. A) At an ISI of 2ms the resultant MEP is inhibited from that of a single pulse alone. B) At an ISI of 12ms the conditioned MEP is facilitated from the single pulse MEP.

After stroke the levels of SICI in each hemisphere are altered. The magnitude of shifts in SICI relates to degree of functional recovery; individuals with better functional ability show higher level of contralesional SICI[74]. Altering SICI and ICF via TMS may be one method by which the brain is restored to a more balanced state. In turn, shifts in intra- and interhemispheric excitability may facilitate greater hemiparetic arm function. Transcallosal inhibition (TCI) refers to the amount of inhibition one hemisphere is exerting on the other. TCI is measured by contracting the target muscle in the arm ipsilateral to stimulation. The length of time an EMG response is suppressed for after a single suprathreshold stimulus is then recorded[15]. After stroke the levels of TCI are altered depending on the location of the stroke[16].

In the present study we investigated a modified version of the Orth paired pulse TMS [79] protocol in a group of participants with chronic stroke. We tested SICI and ICF before and after three days of inhibitory cTBS over the contralesional hemisphere. It was hypothesized that cTBS would facilitate an increase in contralesional SICI and a decrease in the ipsilesional SICI.

Further, it was expected that the level of TCI exerted on the ipsilesional hemisphere by the contralesional hemisphere would be decreased as evidenced by a shortening of the ipsilateral silent period.

3.2 Methods

Experimental Overview

The study involved a cross-over design with each arm of the intervention representing 2 different types of stimulation, active cTBS and sham cTBS delivered over M1. Importantly, each session of brain stimulation was paired with skilled motor practice of a novel motor task. All participants performed a total of 6 cTBS plus practice sessions. These were split into 2 arms in which one variant of cTBS was delivered (active or sham). Following a 2-4 week washout period the opposite form of stimulation was delivered. Paired pulse measures were performed at sessions 1, 5, 6, and 10; sessions 5 and 10 coincided with no-cTBS retention testing. Repetitive TMS was performed at sessions 2-4 and 7-9. All participants had previously undergone an anatomical MRI during other research studies with the lab. These scans were used during TMS sessions to guide coil placement.

Participants

10 individuals (8 male, age 68.3±8.02 years) post stroke were recruited from the local community. All gave written informed consent and the study protocol was approved by the UBC Clinical Research Ethics Board. Participant information is presented in table 2.

Table 2: Participant demographics

Participant No.	Age	Gender	Time Poststroke*	Fugl-Meyer	Presence of ipsilesional MEP	Lesion Location
01	59	M	3	66	+	R Pons
02	67	M	5	51	+	R Basal ganglia
03	77	M	7	36	-	R MCA territory
04	65	M	5	63	+	R Basal Ganglia
05	68	F	11	28	-	R MCA territory
06	76	M	16	32	-	R Basal Ganglia
07	58	M	20	50	+	L MCA territory
08	64	M	4	59	+	R Insular cortex
09	83	M	3	54	+	R Insular cortex
10	66	F	11	63	+	R Insular cortex
Mean	68.3			50.2		
SD	8.02			13.73		

* In years, Fugl-Meyer upper extremity portion only (maximum = 66), MCA = middle cerebral artery, + = MEP present, - = MEP not present

Electromyography Recordings

Surface EMG was recorded from the extensor carpi radialis (ECR) of both arms using Ag/AgCl electrodes. The EMG signal was filtered with a high pass filter (0.3Hz) and notch filter (60Hz) using Power Lab (AD Instruments, Colorado Springs). Data was recorded using LabChart 7 (AD Instruments, Colorado Springs) and analyzed using custom LabView software (National Instruments, Austin, TX).

Transcranial Magnetic Stimulation

Each participant's anatomical MRI was loaded in Brainsight (Rogue Research, Montreal) to allow for sterotaxic guidance of the TMS coil. Magnetic stimuli were delivered with a hand held figure-of-8 coil (diameter 70mm) via two Magstim 200 stimulators connected with the BiStim 2 module (Magstim, Wales). Brainsight, along with EMG recordings was used to

determine the 'hotspot' for ECR. To reduce variability in stimulation targeting this location was marked with a trajectory to ensure all recordings were performed at the same site and angle.

Motor Threshold

Resting motor threshold (RMT) was defined as the minimum stimulus intensity required to evoke an EMG response of at least 50μV in 5 of 10 trials with the ECR at rest. Active motor threshold (AMT) was defined as the minimum intensity required to evoke a response of at least 200μV in 5 of 10 trials with the ECR contracted to 20% maximum voluntary contraction (MVC). Participants were given visual feedback of EMG activity and a target to ensure constant contraction.

Paired Pulse

All paired pulse measures were performed with the participant seated in a modified dental chair with the target muscle at rest. Test stimulus (TS) intensity was determined as the stimulator output that evoked an MEP of ~1mV. If an MEP of ~1mV could not be achieved the intensity at which increasing intensity did not yield an increase in MEP size was chosen. Conditioning stimulus intensity (CSI) was varied and delivered at 15, 35, 55, 75, 95, 105, and 125% of AMT. To test SICI the interstimulus interval (ISI) was set to 2ms, for ICF the ISI was set to 12ms. A train of 64 stimuli was delivered, 8 at each CS intensity and 8 at TS alone, for each ISI. The order of intensities was randomized.

Transcallosal Inhibition

To examine TCI, stimulator intensity was set to 150% of RMT. The ECR ipsilateral to the stimulating coil was contracted to 50% MVC. 12 stimuli were delivered and EMG was recorded from both the contralateral resting limb and the ipsilateral contracted limb.

Repetitive TMS

Participants were counter balanced to receive either active or sham continuous theta burst stimulation (cTBS) on all sessions in between paired pulse sessions. Assignment was made to the first stimulation type, and all participants were then crossed over to receive the opposite type of stimulation after a 2-week washout period. 600 pulses were delivered at 80% AMT over the previously determined target for ECR in the contralesional hemisphere. During cTBS 3 pulses were presented at 50Hz every 200ms for a total of 40sec[21]. Sham cTBS was applied with an inactive coil that looks and sounds like an active coil but does not deliver any stimulation. All participants were naive to TMS measures and were not explicitly informed of the sham condition. cTBS was immediately followed each day by practice of the Functional Hand Task (FHT; see Chapter 2 for detailed description).

Data Analysis

The MEP values from each conditioning stimulation intensity (CSI) were averaged. Trials exceeding two standard deviations of the mean MEP amplitude at each CSI were identified and excluded (<5% for each conditioning stimulus at each ISI) (Edwards et al, in press). Data at each CSI were normalized to the preceding CSI to calculate change in MEP amplitude with increasing stimulation intensity. Change scores were then calculated from pre testing to retention testing for each ISI and hemisphere.

Visual inspection of histograms verified that data were not normally distributed. To account for this we performed nonparametric Wilcoxon Signed Ranks Test on the change scores from pre to retention testing for SICI and ICF in the ipsilesional and contralesional hemispheres.

Transcallosal inhibition was measured in the ECR ipsilateral to the stimulated hemisphere and was defined as a reduction in amplitude of at least 30% from baseline activity

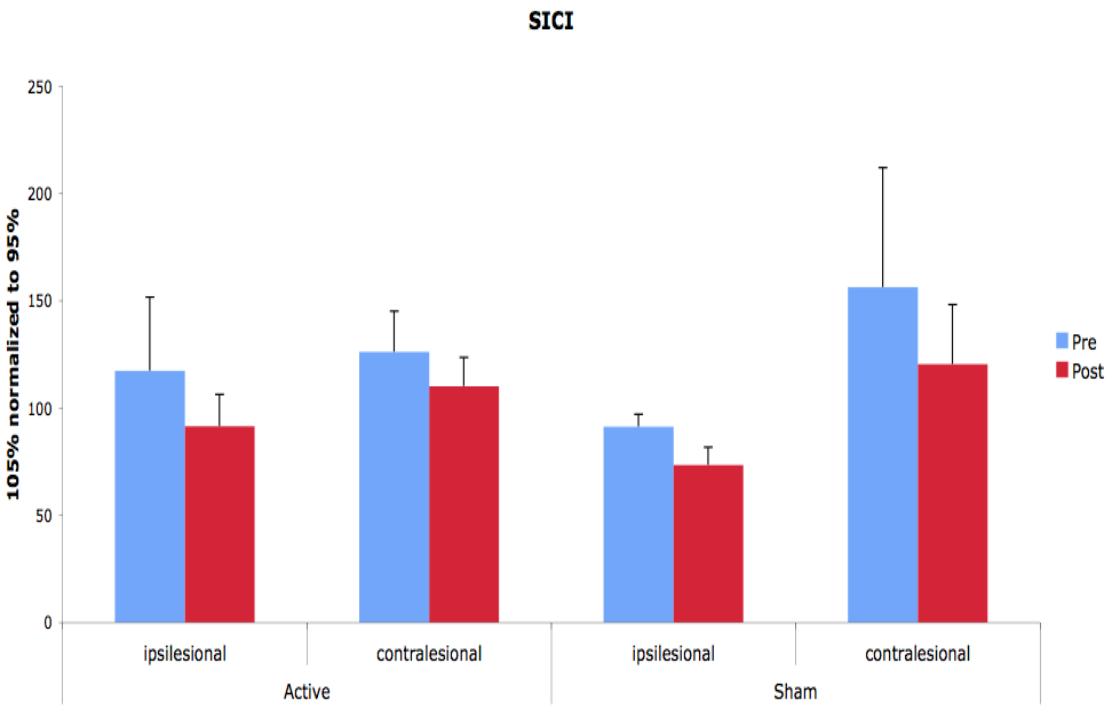
within 30 to 60ms after stimulation[80]. The length of this suppression was referred to as the ipsilateral silent period and its time in ms was recorded. TCI data were not normally distributed. Wilcoxon Signed Ranks Tests were performed on the difference in ipsilateral silent period length from pre testing to retention testing.

3.3 Results

Data from participant 01 had to be excluded from ppTMS analysis due to methodological issues. Participant 03 chose not to continue with the study after the first arm of the cross-over due to family issues and is not included in the following analyses. Due to an inability to elicit an MEP from the ipsilesional hemisphere and perform the FHT participants 05 and 06 were not included in data analysis. No ipsilateral MEPs were recorded from any participants.

Change scores for SICI and ICF for each hemisphere are shown in figure 9. Data are presented for CSIs of 105% normalized to 95% and 75% normalized to 55%. These values were chosen for two reasons: 1) we noted high variability at the lower CSI values of 15% and 35% and 2) 125% AMT approximates RMT and thus elicits an MEP from the CS. There were no significant differences noted with Wilcoxon Signed Rank testing for SICI and ICF from pre testing to retention testing for either hemisphere or ISI at either CS intensity. Because the numbers of participants included in this data set was low (n=6), we assessed the clinical meaningfulness of the data using Cohen's d. Effect sizes were calculated from pre testing to retention testing at each ISI for each hemisphere. After active stimulation there was a large effect size in the unaffected hemisphere for ICF at 105% (Cohen's d=-1.44) and a moderate effect at 95% (Cohen's d=-0.43) revealing a decrease in facilitation in the stimulated, contralesional hemisphere.

A



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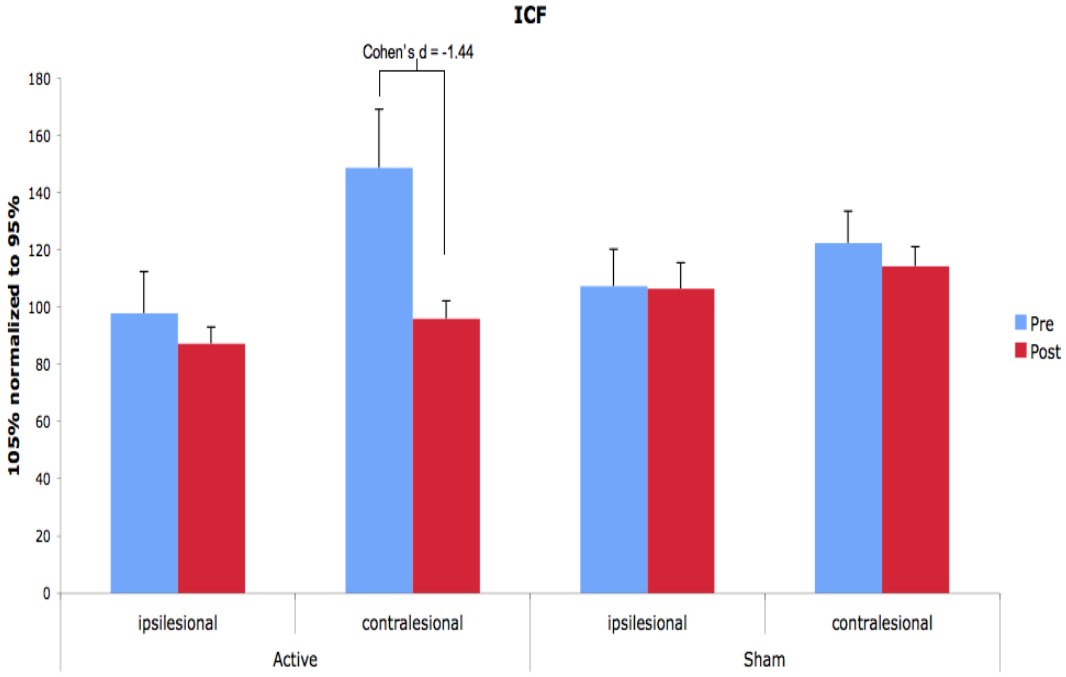

Figure 9: Paired pulse TMS data for 105% AMT normalized to 95% AMT. A) SICI did not reveal any significant differences from pre to retention testing in either hemisphere after active or sham stimulation. B) ICF also did not reveal any significant differences however there was a large effect size for a decrease in facilitation in the contralesional hemisphere after active stimulation. SE bars are shown.

TCI data did not reveal any significant differences in the change from pre testing to retention testing after either active or sham stimulation. Effect size testing shows a moderate effect size in the hemiparetic arm after active stimulation (Cohen's d=-0.47) indicating a shortening of the ipsilateral silent period. After sham stimulation the effect size for the change in the non-hemiparetic arm was small (Cohen's d=-0.26) (Figure 10). This shows less inhibition is being sent from the contralesional hemisphere to the ipsilesional hemisphere after active stimulation.

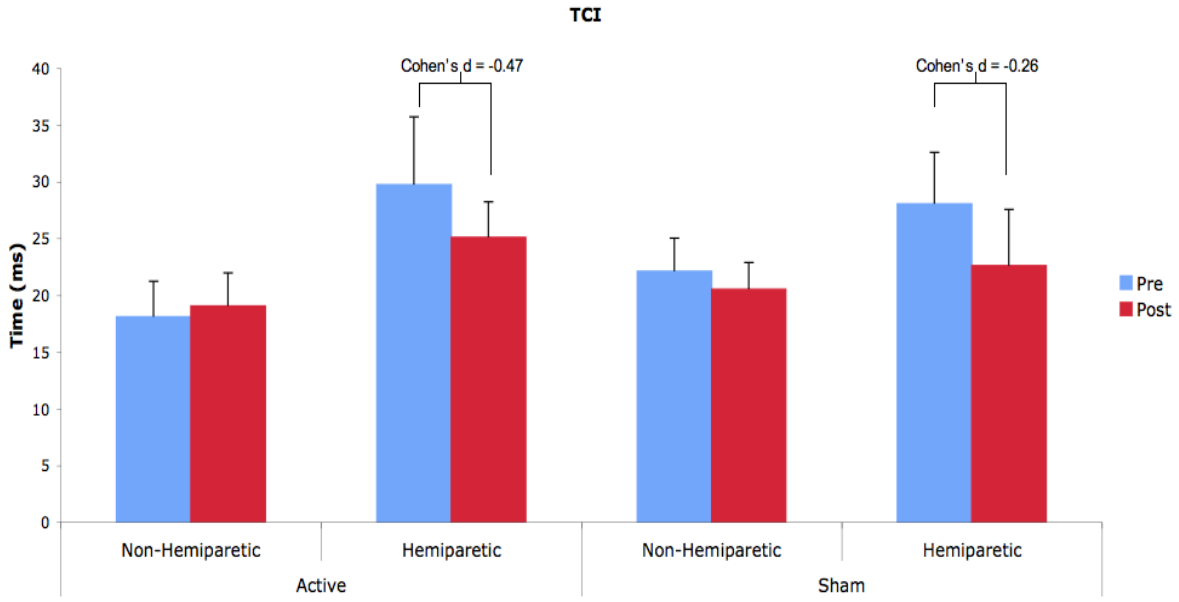

Figure 10: Ipsilateral silent period length. After active stimulation a moderate effect size for a shortening of the ipsilateral silent period in the hemiparetic arm suggests decreased inhibition from the contralesional to the ipsilesional hemisphere.

3.4 Discussion

To our knowledge, this is the first study to assess the effects of multiple days of stimulation plus skilled motor practice on the excitability of the primary motor cortices. Thus far, the majority of studies have examined motor cortical excitability immediately after one session of stimulation and/or in the absence of skilled practice[58, 70, 75, 81]. The current work advanced past findings by pairing skilled motor practice over 3 days with cTBS. With this approach it was noted using effect sizes that excitability in the contralesional hemisphere is reduced and TCI is decreased from the contralesional hemisphere to the ipsilesional hemisphere.

Unlike previous studies of motor cortical excitability that used ppTMS, we held the interstimulus interval constant and changed the intensity of the conditioning stimulus. This allowed us to examine how SICI and ICF changed over a range of stimulus intensities from 15% AMT up to 125% AMT. This approach to assessing intracortical excitability does not assume that all participants show the same thresholds for inhibition and facilitation. Previous studies have used set values of 80% RMT and 120% RMT as their CS and TS. These values may be higher or lower in some participants than what is needed to induce inhibition or facilitation. Further, because the determination of RMT is less reliable than AMT[79] the traditional method of holding CSI constant may yield more variable data[79].

We chose to analyze our data differently than Orth et al.[79]. Rather than generating a curve of percent SICI and ICF for all CSIs, we assumed a linear relationship between each CSI and examined the changes that occurred between each of them. The reasoning for this was to observe how the MEPs elicited at each CSI related to the ones preceding it. This allowed us to compare paired pulses to paired pulses rather than comparing to a single pulse as in previous paired pulse studies[77, 78]. After active cTBS we found moderate and large effect sizes suggesting a decrease in facilitation in the contralesional hemisphere. A decrease in facilitation in one

hemisphere has previously been found to relate to increases in excitability in the contralateral hemisphere. Though we were not able to show these effects at a delayed retention test it may be that immediately after stimulation the effects were present. In individuals with stroke, enhanced excitability of the ipsilesional hemisphere has been linked to performance gains in the hemiparetic arm[63, 81]. We also showed a moderate effect size for the reduction of TCI from the contralesional to ipsilesional hemisphere. Taken together, these results suggest that cTBS has lasting inhibitory effects on the stimulated hemisphere and that these effects are transferred via to the corpus callosum to the unstimulated hemisphere

cTBS is thought to exert its effects through NMDA receptors, which have been shown to be related to ICF[14, 82, 83]. Our results suggest that there is a decrease in facilitation of the stimulated hemisphere that lasts well beyond the immediate delivery of cTBS. These lasting changes are likely a result of cTBS inducing long-term potentiation and depression (LTP, LTD) in the motor cortex[84]. As individuals recover from stroke, a shift in excitability from the contralesional to ipsilesional hemisphere has been shown[31, 32] and the higher levels of excitability in the ipsilesional hemisphere have been associated with better recovery[16, 74].

Contrary to our initial hypothesis we did not demonstrate a change in the levels of SICI or ICF in the ipsilesional hemisphere. A likely explanation for this is that our paired pulse testing sessions occurred 24 hours after the last cTBS session. The effects of cTBS are thought to last for approximately 1 hour[22] thus any residual effects on the ipsilesional, un-stimulated hemisphere may not have persisted to retention. Though the effects were likely present each day, by retention testing they may have simply worn off. Had more days of stimulation and practice been given it is possible the effects would have lasted to retention testing. Another possible explanation surrounds the stimulation parameters that were chosen. cTBS is delivered at a very low intensity (80% AMT) and it has been suggested that this is not strong enough to

activate cross callosal fibers[37], although contralateral changes in SICI and ICF have been recorded in healthy participants[85]. By increasing the stimulation intensity it is possible that changes would be induced in the ipsilesional hemisphere.

A limitation in the current study is the low number of participants. Our moderate and large effect sizes suggest that given more participants it is likely that many of the measures would have reached statistical significance. An additional source of variability that was discovered during data collection was the participant's level of alertness. When a participant became sleepy the size of the MEP collected visibly dropped off. Steps were taken to try to ensure consistent alertness during testing. SICI and ICF have been shown to change during different stages of sleep[86] indicating the importance of ensuring participants are fully awake during paired pulse recordings.

In sum, we found moderate to large effect sizes for a decrease in facilitation in the stimulated, contralesional hemisphere after 3 days of inhibitory cTBS. Importantly, these effects were present 24 hours after the last bout of stimulation was received suggesting that multiple days of cTBS cause long lasting changes in the excitability of the cortex. There was also a moderate effect size for reduction in transcallosal inhibition from the contralesional to ipsilesional hemisphere. This reduction in inhibition may be linked to improvements in performance of a novel task that were noted when cortical stimulation is paired with task practice (see chapter 2 of this thesis). Future studies should examine the effects of cTBS on excitability after each stimulation session. This would provide a more complete picture of the cumulative effects of multiple days of stimulation on cortical excitability.

CHAPTER 4: Conclusions and general discussion

4.1 Introduction

Every year in Canada more than 50,000 people will have a stroke. Of those 65% are left with lasting impairments[3]. After the initial recovery period has ended stroke patients are left with few options to improve their level of function. The main aim of rehabilitation is the restoration of function. Transcranial magnetic stimulation (TMS) is one method that may facilitate recovery of arm function by priming the brain for neuroplastic change. Thus, it may be that combining brain stimulation with rehabilitation therapy may enhance functional gains when compared to therapy alone. Previous studies have examined the effects of TMS on function immediately after stimulation[24, 37] and after multiple days of stimulation[36, 63] but have not examined the combined effects of stimulation and skilled motor practice.

The purpose of this thesis was to pair TMS with skilled practice of a novel motor task and examine capability for motor learning, changes in function, and alterations in electroneurophysiology in M1. This chapter will summarize the main results from the previous chapters and provide an overview of cortical excitability and motor learning following stroke. Lastly, the limitations of the current studies and directions for future research will be discussed.

4.2 Summary of Results

Functional Hand Task

Past motor learning studies have shown that the ability to learn a motor task is not lost after stroke[39, 42, 87]. fMRI studies have shown that the primary motor cortices are activated bilaterally after stroke with use of the hemiparetic arm[30, 31] and it has been suggested that the

increased activation in the contralesional cortex is detrimental to performance. I used cTBS to reduce contralesional motor cortical excitability before practice of the FHT. At retention testing (after 3 days of stimulation) participants who received active cTBS had faster response times than those who received sham stimulation. There was also improvement in the functional measures of blocks to box and a subset of items from the Jebsen-Taylor Hand Function Test (feeding, writing). This finding is in agreement with Fregni et al.[36] who showed that participants who received inhibition of the contralesional motor cortex via 1Hz rTMS showed larger improvements in functional measures than those who received sham stimulation. M1 is involved in the consolidation of newly learned movements[88]. This thesis shows that the combination of cTBS to M1 and skilled motor practice facilitates sequence specific implicit learning and not just improvements in generalized motor performance.

Cortical excitability

It has been demonstrated that there are changes in the levels of SICI and ICF in both hemispheres after stroke[74]. I aimed to alter these imbalances with inhibitory stimulation of the contralesional hemisphere. The effect sizes of the changes I observed suggest that multiple days of inhibitory stimulation decrease facilitation in the stimulated, contralesional hemisphere. There was also a large effect size for a decrease in intercortical inhibition from the contralesional to the ipsilesional hemisphere showing that cTBS over the contralesional hemisphere had reduced the magnitude of transcallosal inhibition being placed on the ipsilesional motor cortex.

Taken together these results suggest that cTBS over the contralesional hemisphere does impact both local motor cortical excitability and transcallosal inhibition. I speculate that it was the decrease in inhibition after active stimulation that allowed the participants to show sequence-

specific motor learning of the FHT and larger improvements in some measures of functional ability as compared to sham stimulation.

4.3 Cortical Excitability and Motor Learning After Stroke

Confirming the benefit of practice for motor learning after stroke, all participants improved on the random portion of the FHT regardless of stimulation condition. Importantly, I also noted decreases in SICI after sham stimulation plus skilled motor practice showing that, as others have suggested, meaningful practice alone can cause plastic changes in the cortex after stroke[89] and alter cortical excitability. The addition of cTBS enhances the net effect of task practice alone. The combination of stimulation and task practice causing increased performance may be explained by Hebbian learning[98]. By stimulating the synapse through both cTBS and repetitive task practice the strength of individual synapses may have been heightened. Kobayashi[90] was able to show improved performance on a finger tracking task in healthy participants after inhibiting the hemisphere ipsilateral to the hand being used to track. I have extended this work into the stroke population and am able to confirm the finding of improved sequence specific performance with the hand ipsilateral to stimulation.

Inhibition from the contralesional hemisphere to the ipsilesional hemisphere is increased after stroke[28, 34, 91]. The results of this thesis and previous work[28, 34, 36, 91] suggest that increased inhibition is one possible mechanism for impaired motor performance with the hemiparetic limb. Reductions in IHI correlate with improvements in motor function[74]. By reducing the inhibition being sent from the contralesional hemisphere to the ipsilesional hemisphere the ipsilesional hemisphere is effectively 'released' allowing it to inhibit the contralesional hemisphere. This restoration in balance may be an important aspect of stroke rehabilitation. Ward et al.[47] showed with fMRI that a focusing of activation from a bilateral pattern to the ipsilesional hemisphere is

associated with functional improvements. TMS may be a useful tool to assist in refocusing activation in the ipsilesional hemisphere after stroke.

Boyd et al.[41] found a severity effect in the ability to learn an implicit task following stroke. Their study was performed using the non-hemiparetic arm showing a diminished capacity for implicit learning even when the functionality of the hemiparetic arm is not a factor. This is one possible explanation for the inability of 2 participants in this thesis to perform the FHT. Both were more severely affected than the other participants (FM < 35) suggesting that there may be a minimal functional requirement for participants in TMS and motor learning studies.

4.4 Limitations

Participants

One of the limitations of this thesis is the low number of participants involved. Though only 7 were included in the analyses presented in Chapter 2, and 6 in Chapter 3, 10 participants enrolled in the thesis study. Sample size calculations based on effect size testing of intracortical excitability (Cohen's d = .93) demonstrate that at least 12 individuals would be required to reach statistical significance ($p<.05$)[99]. Figure 11 shows a flow chart of the difficulties encountered with recruitment and data collection. The inability to record an MEP from the ipsilesional hemisphere is an issue that has been reported previously in the literature[70]. Stinear et al.[92] suggest that an inability to elicit an MEP is correlated with decreased functional potential. The participants in this thesis in whom an MEP could not be elicited were unable to perform the FHT (Figure 10).

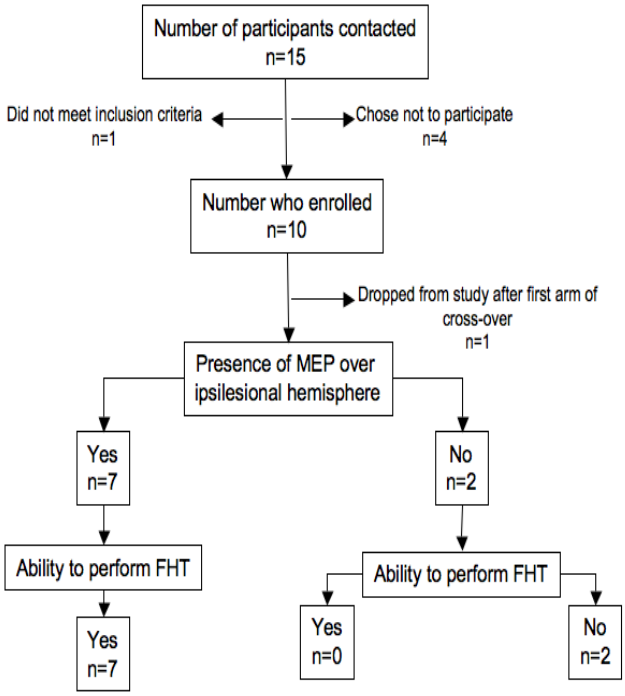

Figure 11: Participant recruitment and enrollment flowchart

Accelerometers

Accelerometers were used to determine whether the participants increased their arm use after either active or sham stimulation compared to baseline values. Importantly, there were no differences in the amount of hemiparetic arm use outside of our intervention during the wash-out phase between stimulation types as compared to pre-testing. One drawback of accelerometers is that they do not denote what types of movements are taking place so the researcher is unable to distinguish between functional tasks (e.g. picking up a cup, brushing hair) and non-functional movements (e.g. swinging motions during walking)[93].

Functional Hand Task

The items of the FHT were chosen because they represented items that would be meaningful to the participants and could be performed by individuals who were more severely affected by stroke. One draw back of this task however, is the lack of control of how each individual interacted with the objects of daily life during practice. I noted that participants activated the items in a different manner, some opening their hand fully during turning a door handle for example while others used a closed fist. Additionally, in the FHT there is not a home button to control the starting location of the hand at the beginning of each trial. Thus, some brought their hemiparetic hand back to their lap after each response whereas others kept it in the air so they were able to respond faster to the next stimulus. The choice of where the hand was kept between trials appeared to be determined by arm function with individuals with higher functional capability maintaining the arm in the air between responses. Arm position did not appear to change within participants across days of testing, however, as we did not explicitly test this issue it did add variability to response times, likely both between and within subjects.

4.5 Future Research

Participants and Stimulation Parameters

Lesion location may differentially affect the ability of stroke participants to learn motor tasks. Future studies should examine a larger group of stroke participants subdivided into cortical and subcortical stroke locations to give a better understanding of how stimulation paired with learning affects each group. Additionally, by stratifying the participants by stroke severity researchers could investigate whether stimulation is a therapy that is better able to assist mild, moderately, or severely affected patients.

The effects of different types of inhibitory stimulation have not been well documented. Bringing the same participants back for a third cross-over arm to compare the effects of cTBS to traditional 1Hz inhibitory rTMS would also help to inform researchers of the effects of different types of stimulation. Differences in cTBS and 1 Hz rTMS have been examined after one session but the cumulative effects of multiple days have not been considered. As previously suggested it is also possible that cTBS at 80% AMT may not be strong enough to effectively activate cross callosal connections[37], thus it would be beneficial to test in a group of participants the effects of stimulation at 90% and 100% of AMT.

Task Practice and Cortical Excitability

The number of training sessions needed to generate lasting cortical excitability is still not known. Studies of motor learning range from one day[24, 63, 94] to multiple weeks[95-97] in length with a varying amount of practice within each session. Extending the current study to 5 days likely would have resulted in even greater improvements in performance. Though the effects of stimulation on cortical excitability have been previously measured directly after stimulation[70, 75] it would be valuable to examine the cumulative effects from multiple days of stimulation as well as the effects immediately after performing a motor learning task.

TMS and Rehabilitation

It has been proposed that TMS could be used as an adjunct to rehabilitation[36, 70, 89]. The results of this thesis have established that multiple days of stimulation paired with skilled motor practice can not only enhance learning of a novel motor task but also improve performance on standardized measures of function. This information is valuable to researchers and therapists alike, as the possibility of combining stimulation with therapy to enhance treatment in the

chronic stage of stroke seems promising. Randomized controlled trials of TMS and therapy should be the next step in establishing the feasibility of such a combination.

4.6 Conclusion

Overall, the results of this thesis suggest that continuous theta burst stimulation enhances performance on a novel motor learning task. It has expanded on previous work by differentiating between improvements of generalized motor control and implicit motor learning, a concept previously unexamined after the application of TMS. Additionally, it is the first work to combine multiple days of task practice with stimulation and examine the effects of this combination on electroneurophysiology. By inhibiting contralesional M1 I was able to facilitate implicit sequence specific motor learning. This improvement in performance on the FHT was strongly correlated with improvement on the blocks to box task, a measure of function in the hemiparetic arm after stroke. Large effect sizes also suggest that the level of inhibition from the contralesional hemisphere to the ipsilesional hemisphere was decreased following the combination of stimulation and task practice. Taken together, these results demonstrate the viability of TMS as an additional tool for rehabilitation specialists.

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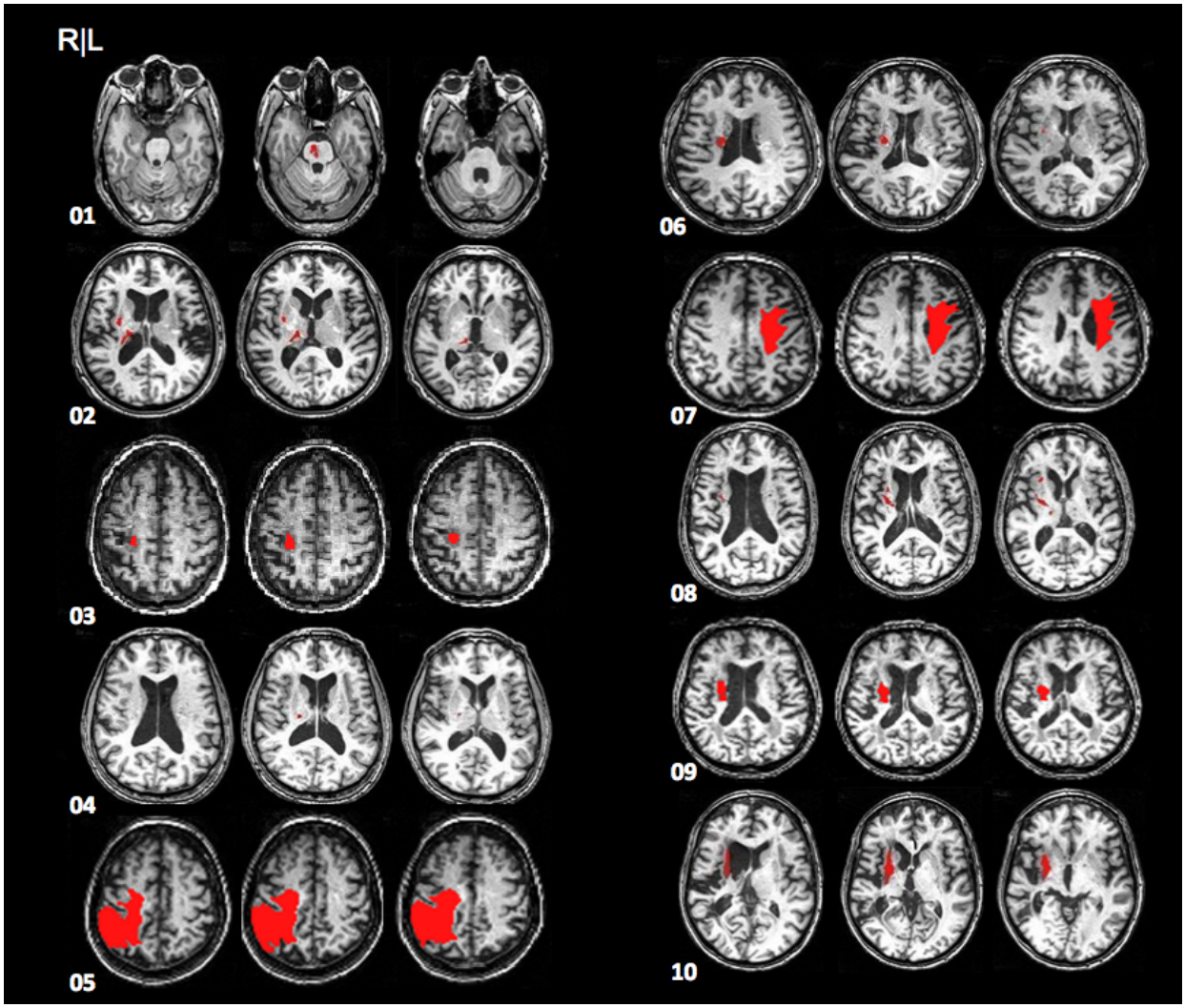
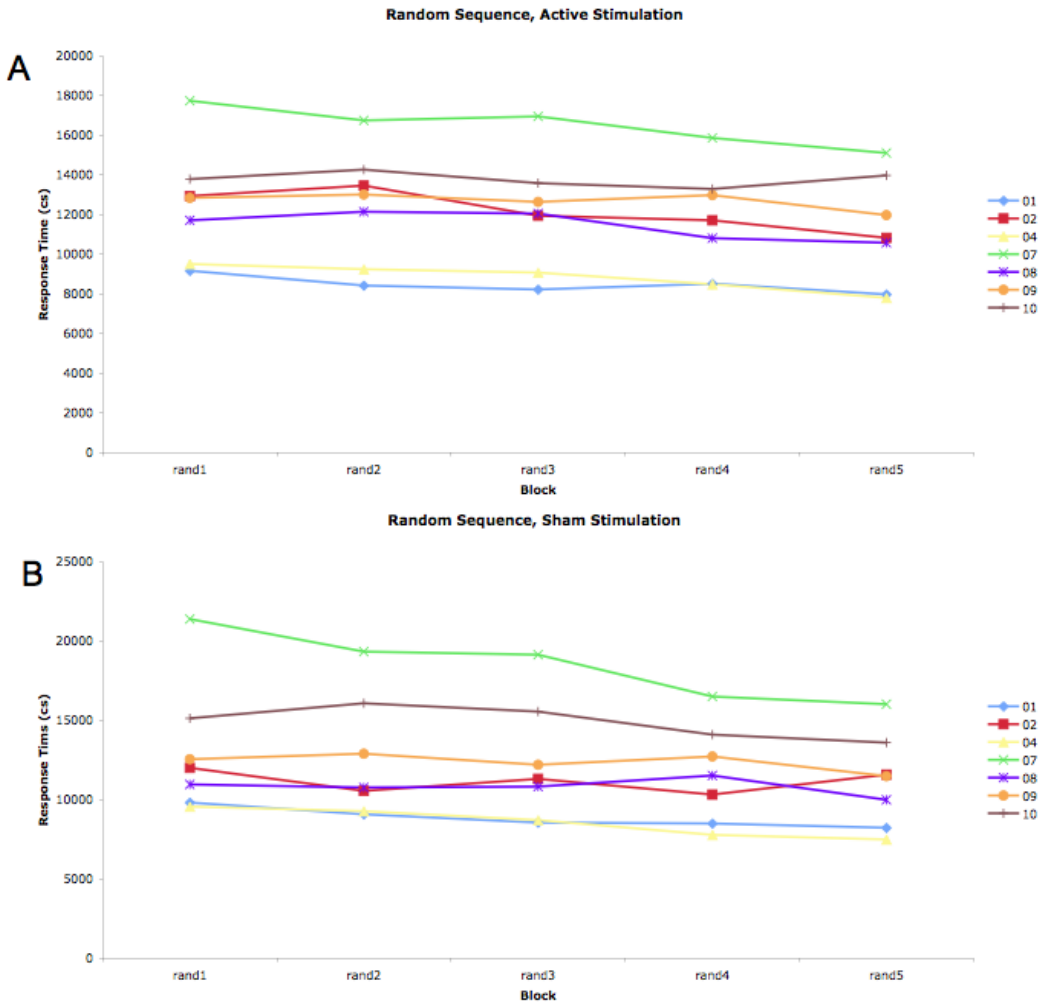
APPENDIX 1: Participant lesion locations

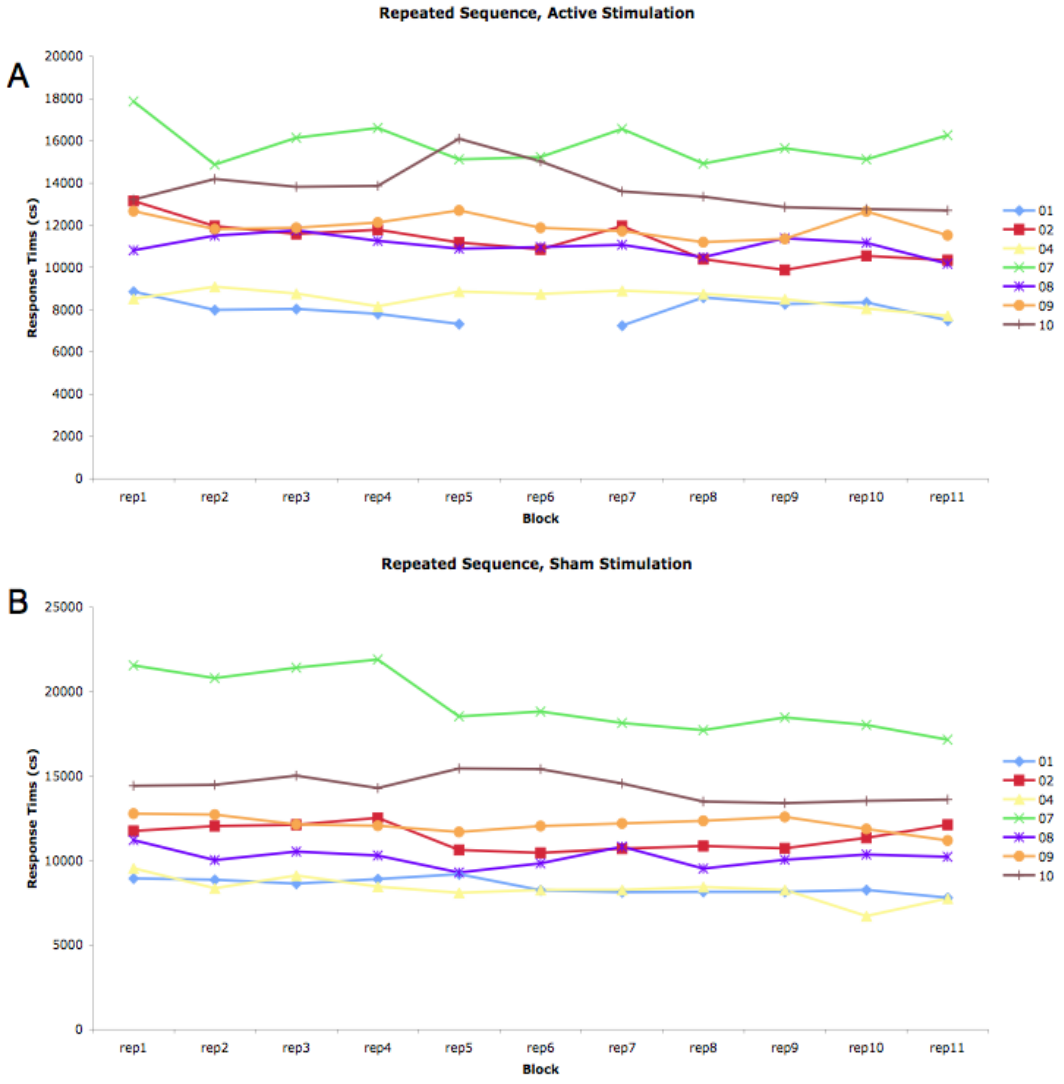


Individual participant lesion locations. The center image for each participant indicates the largest portion of the lesion. The first and third images for each participant are ± 4.5mm away from the center image and are included to show the extent of the lesion.

APPENDIX 2: Individual participant FHT data



Individual participant data for the FHT on the random sequence after A) active stimulation and B) sham stimulation.



Individual participant data for the FHT on the repeated sequence after A) active stimulation and B) sham stimulation.

APPENDIX 3: Randomization order

Participant	First Stimulation Condition	First FHT Box
401	active	1
402	active	1
403	sham	1
404	sham	1
405	active	2
406	sham	1
407	sham	2
408	active	2
409	active	1
410	sham	2

Randomization order for stimulation condition and the box received during the first arm of the cross-over.

APPENDIX 4: Functional data

Functional measures change scores. Data are presented post - pre. Positive values show improvement for Blocks to Box, and Grip Strength
Negative values indicate improvement for all measures of the Wolf Motor Function Test

ACTIVE

	Blocks to Box		Grip Strength		Wolf Motor Test Can		Paper Clip		Towel		Wolf Total	
Participant	Non-Hemi	Hemi	Non-Hemi	Hemi	Non-Hemi	Hemi	Non-Hemi	Hemi	Non-Hemi	Hemi	Non-Hemi	Hemi
401	2.00	4.00	2.00	0.00								
402	2.00	4.00	10.33	0.33								
403												
404	3.00	5.00	8.67	4.00	0.09	-0.13	0.70	-0.14	0.06	-0.06	0.85	-0.33
405	2.00	0.00	2.33	0.67	0.02	0.00	-0.37	0.00	-1.28	66.00	-1.63	66.00
406	-7.00	2.00	-2.00	0.33	0.02	116.50	-0.31	0.00	-0.47	-0.15	-0.76	116.35
407	-2.00	5.00	-0.33	3.00	0.15	-0.13	-0.14	-0.47	-0.09	0.37	-0.08	-0.23
408	3.00	4.00	-2.00	5.33	-0.34	-0.03	-0.01	-0.59	-1.75	-2.41	-2.10	-3.03
409	8.00	3.00	-0.33	-1.33	-0.10	-0.01	-0.46	-0.28	-0.12	0.69	-0.68	0.40
410	1.00	1.00	-0.33	-0.33	-0.46	-0.03	-0.09	-0.09	-0.91	-0.31	-1.46	-0.43

SHAM

	Blocks to Box		Grip Strength		Wolf Motor Test Can		Paper Clip		Towel		Wolf Total	
Participant	Non-Hemi	Hemi	Non-Hemi	Hemi	Non-Hemi	Hemi	Non-Hemi	Hemi	Non-Hemi	Hemi	Non-Hemi	Hemi
401	-4.00	-8.00	1.67	5.00								
402	4.00	-4.00	0.67	0.67	0.12	-0.03	0.11	0.47	-0.96	-0.16	-0.73	0.28
403												
404	4.00	2.00	-6.00	-2.00	-0.12	-0.16	0.73	0.22	-1.44	-1.00	-0.83	-0.94
405	-1.00	0.00	1.67	0.00	0.18	0.00	-0.72	0.00	-1.72	0.00	-2.26	0.00
406	7.00	5.00	-1.67	-0.67	-0.03	-2.00	-0.12	0.00	1.87	-4.25	1.72	-6.25
407	5.00	-2.00	1.33	0.67	0.22	-0.09	0.20	-1.37	-0.02	0.50	0.40	-0.96
408	6.00	-3.00	-1.33	1.00	-0.25	-0.19	0.59	0.72	-2.31	-1.02	-1.97	-0.49
409	0.00	0.00	0.67	-1.67	0.16	0.25	0.08	0.20	-0.50	0.05	-0.26	0.50
410	-4.00	-5.00	-1.00	-2.00	0.22	0.13	-0.16	0.04	0.07	1.23	0.13	1.40

Jebsen-Taylor Hand Function Test change scores. Data are presented as post - pre. Negative values indicate faster performance.

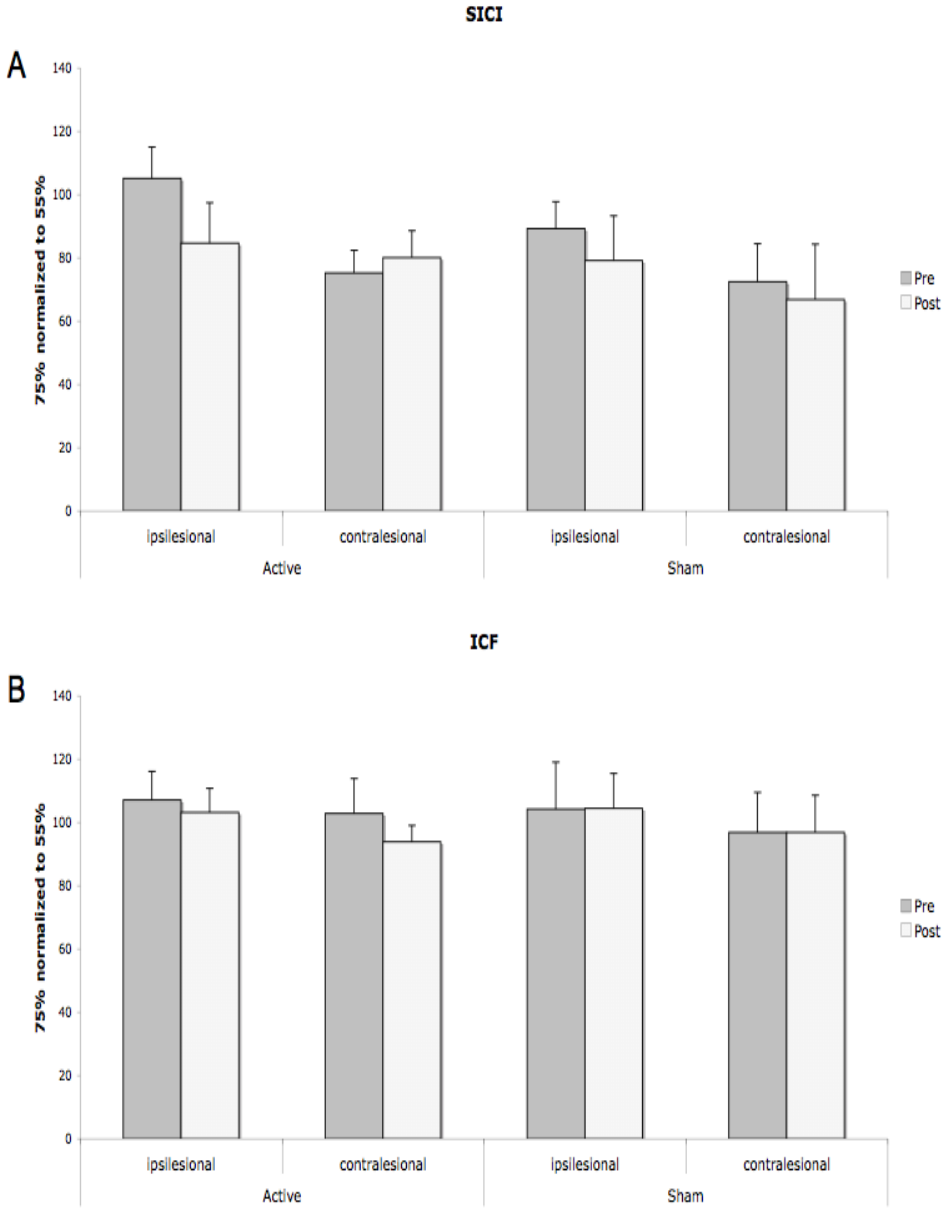
ACTIVE

	Jebsen *Writing*		*Page Turning*		*Lifting Small Objects*		*Simulated Feeding*		*Stacking Checkers*		*Lifting Large Light*		*Lifting Large Heavy*		*Total Time*	
	Hemi	Non-Hemi	Hemi	Non-Hemi	Hemi	Non-Hemi	Hemi	Non-Hemi	Hemi	Non-Hemi	Hemi	Non-Hemi	Hemi	Non-Hemi	Hemi	Non-Hemi
401	-1.51	-1.75	0.34	-0.75	0.94	-0.28	0.66	-1.37	1.93	-0.21	-0.21	0.19	-0.13	0.24	2.02	-3.93
402	-3.44	-1.72	-0.82	-0.82	1.60	-0.84	-5.51	-3.04	-1.25	-1.25	-0.46	-0.40	-1.62	-0.57	-11.50	-8.64
403																
404	-1.15	-0.93	-0.21	0.04	-0.08	0.29	-3.97	2.64	-1.04	-1.74	0.04	-0.25	0.19	0.19	-6.22	0.24
405		0.35		0.14		0.32		-0.75		0.06		0.12		-0.43		-0.19
406	-5.86	-1.50	-0.91	-0.75	-21.21	-0.56	-9.57	-0.40	-18.59	0.06	-34.91	-0.52	-5.04	-0.51	-96.09	-4.18
407	1.17	0.44	-2.69	-0.13	1.23	-1.28	-12.56	1.04	-2.90	1.44	0.19	-0.34	-1.66	-0.03	-17.22	1.14
408	-1.25	0.09	2.71	1.79	-4.16	-0.37	-4.27	-1.88	0.64	-1.12	0.18	0.03	-0.03	0.75	-6.18	-0.71
409	-0.60	3.62	-0.01	-0.32	-2.00	1.16	-0.98	-2.76	-2.88	0.95	-0.81	-0.03	-0.02	-0.66	-7.30	1.96
410	-5.74	-0.34	0.47	0.03	0.24	0.35	0.80	-0.47	-0.05	-0.37	-0.13	0.05	-0.88	-0.66	-5.29	-1.41

SHAM

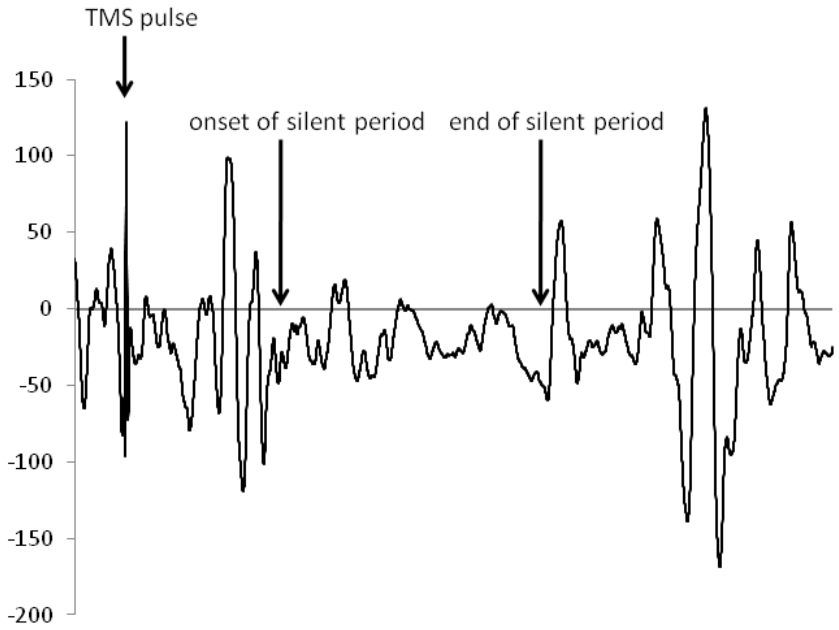
	Jebsen *Writing*		*Page Turning*		*Lifting Small Objects*		*Simulated Feeding*		*Stacking Checkers*		*Lifting Large Light*		*Lifting Large Heavy*		*Total Time*	
	Hemi	Non-Hemi	Hemi	Non-Hemi	Hemi	Non-Hemi	Hemi	Non-Hemi	Hemi	Non-Hemi	Hemi	Non-Hemi	Hemi	Non-Hemi	Hemi	Non-Hemi
401	2.10	2.57	-2.31	0.30	-0.19	-0.63	-0.65	0.93	0.56	-0.66	-0.15	-0.37	-0.24	-0.03	-0.88	2.11
402	-0.74	-0.21	-1.34	0.15	-6.16	-0.68	-1.03	-0.98	2.93	-0.29	-0.90	-0.44	-0.90	-0.16	-8.14	-2.61
403																
404	3.41	0.60	-0.38	-0.54	-1.81	0.00	-0.75	0.96	3.44	0.65	0.05	-0.16	0.34	-0.15	4.30	1.36
405		-0.97		-0.69		-1.90		-1.30		-1.19		0.66		0.53		-4.86
406	-15.09	0.62	-6.94	-2.06	-1.89	-3.12	-37.50	0.69	-53.79	0.68	-8.91	0.19	1.90	1.81	-122.22	-1.19
407	-9.53	-0.68	1.07	-0.11	-5.54	-1.60	1.03	1.24	-0.82	0.97	-6.56	-0.47	-0.63	0.00	-20.98	-0.65
408	-1.49	-1.96	0.56	0.06	-0.16	-0.78	0.00	0.91	-1.03	0.19	0.16	-0.07	0.10	0.06	-1.86	-1.59
409	4.91	0.65	-1.44	0.27	2.75	-1.28	-2.22	1.13	-0.97	2.91	0.52	0.03	-1.41	-0.54	2.14	3.17
410	-1.00	0.90	0.24	-0.23	-1.37	-0.28	-5.99	0.46	2.16	-0.31	-3.72	-0.23	0.09	0.16	-9.59	0.47

APPENDIX 5: Paired pulse data



Data of 75% AMT normalized to 95% AMT. A moderate effect size for a decrease in facilitation in the contralesional hemisphere is seen after active stimulation. Error bars are SE.

APPENDIX 6: Ipsilateral silent period



Sample trace of TCI as measured by the ipsilateral silent period in the EMG recording of the ECR of the arm ipsilateral to stimulation.

APPENDIX 7: TMS screening form

BRAIN BEHAVIOR LAB
TRANSCRANIAL MAGNETIC STIMULATION (TMS) SCREENING FORM

Below is a questionnaire used to exclude participants considered not suitable for transcranial magnetic stimulation (TMS). This information, as well as your identity, will be kept confidential.
PLEASE COMPLETE FORM BELOW:

Participant Code: _____ **Age:** _____

Please **CIRCLE ONE**:

Neurological or Psychiatric Disorder	YES	NO	Multiple Sclerosis	YES	NO
Head Trauma	YES	NO	Depression	YES	NO
Stroke	YES	NO	treatment with amitryptiline and haloperidol	YES	NO
Brain surgery	YES	NO	Implanted medication pump	YES	NO
Metal in cranium	YES	NO	Intracranial Pathology	YES	NO
Brain Lesion	YES	NO	Albinism	YES	NO
Pacemaker	YES	NO	Intractable anxiety	YES	NO
History of seizure	YES	NO	Pregnant	YES	NO
Family history of epilepsy	YES	NO	Headaches or Hearing problems	YES	NO
History of epilepsy	YES	NO	Family History of Hearing Loss	YES	NO
Intracorporal electronic devices	YES	NO	Other medical conditions	YES	NO
Intracardic lines	YES	NO			

If you answered "yes" to any of the above questions, please provide details below.

_____

_____

APPENDIX 8: Consent form

THE UNIVERSITY OF BRITISH COLUMBIA

School of Rehabilitation Sciences
Faculty of Medicine
T325-2211 Wesbrook Mall
Vancouver, British Columbia V6T 2B5
Phone: 604.822.7392
Fax: 604.822.7624
Web: www.rehab.ubc.ca

Title of Study:

Does inhibition of contralesional areas increase function of the affected upper extremity in individuals with stroke?

Consent Form

Principal Investigator: Lara Boyd, PT, PhD. School of Rehabilitation Sciences, Brain Behaviour Laboratory, Faculty of Medicine, UBC (604) 822-7197

Team Members: Meghan Linsdell, Sean Meehan, Bubblepreet Randhawa, Brenda Wessel, Nicole Acerra, Elizabeth Dao, Jodi Edwards

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Invitation to Participate: As a person who has had a stroke, you are being invited to participate in a research study to determine if learning to move your stroke affected arm can be enhanced by stimulating cortical cells in your brain (non-invasively and without pain).

Participation is Voluntary: You do not have to participate in this research study. It is important that before you make a decision to participate, you read the rest of this form. Please read the following form carefully and ask questions if anything is not clear. The consent form will tell you about the study, why the research is being done, and what will during the study and the possible risks, benefits, and discomforts.

If you wish to participate, you will be asked to sign this form. If you do decide that you would like to participate, you are still free to withdraw at any time and without giving any reasons for your decision. If you do not wish to participate, you do not have to provide any reason for the decision nor will you lose the benefit of any medical care to which you are entitled or presently receiving.

Please take time to read the following information carefully and to discuss it with your family, friends and doctor before you decide.

Purpose

The purpose of this study is to determine whether pairing brain stimulation with rehabilitation helps people recover the use of their stroke affected arm. These efforts should lead to the development of new rehabilitation approaches that can stimulate normal patterns of brain activity after stroke.

Who Can Participate in this Study?

You have been identified because you have had a stroke and you are between the ages of 40 and 85. If you agree to take part in the study, Dr Boyd or her associates will determine if you have any condition that will prevent you from being in the study. Screening should take no more than 5 minutes.

Who Should Not Participate in this Study? You should not participate in this study if you have a history of seizure after your stroke, epilepsy, neurodegenerative disorder, head trauma, a psychiatric diagnosis or limited arm function that you cannot complete the task. If you are younger than 40 or older than 85 you should not participate in this study. If you are pregnant, claustrophobic (have a fear of small spaces), or have metallic objects in your head you should not participate.

What does the study involve?

If you are eligible and decide to participate in this study, you will come to the Brain Behavior Lab for 10 visits. Each of the visits will last about 1.5hours. These sessions can be completed over two 3-week periods. You will also be asked to wear wrist accelerometers for 3 days before the study begins, 3 days in between the different parts of the study, and 3 days after completion of testing. These will be used to count the number and type of activity that you are doing with each of your arms.

Either active Transcranial magnetic stimulation (TMS) or inactive-TMS will be applied over the outside of your head. TMS excites the motor areas of the brain. This excites brain cells non-invasively and without pain. We will use TMS to activate the brain just before each session of rehabilitation for the stroke-impaired arm.

On the first day of this study you will come to the Brain Behavior Laboratory at UBC to sign consent forms and practice the experimental tasks. Your task will involve using your stroke-affected arm to complete a functional task consisting of manipulating a button, door handle, slide lock, and light switch. On each day you will receive 1 minute of stimulation followed by 15 minutes of practicing the functional task

<u>Future studies</u>: You may be invited to take part in future studies. If Dr. Boyd thinks you might qualify for another study by her or her colleagues, she will contact you directly by mail or telephone and ask if you are interested. If you choose not to take part in future studies you should tell her. There will be no impact on you if you choose not to take part. You are not giving permission to do any future studies in this consent form.

Are you willing to be contacted in the future about participation in other studies?
_____ *YES* _____ *NO*

What Are Possible Harms and Side-Effects of Participation

There are potential discomforts and risks to your health and well being if you agree to be a subject in this research. These risks are not greater than the risks in everyday life. These procedures

will be conducted according to published safety standards by Dr. Boyd who has completed procedural and safety training for these procedures at Harvard Medical School and certified in their use. Dr. Boyd or her associates have discussed this research with you and have described them as follows:

Task practice: There are no known risks associated with practicing the functional hand task. However, you may become tired during these tests. In this case you can ask the researchers and you will be able to take a rest. You might also become anxious if you are having difficulty. If you wish, you can tell the researchers that you are uncomfortable at any time and they will stop the testing.

TMS: There is a potential risk of seizure induction in people with a history of seizures (e.g. epilepsy). You will not be eligible to participate in this study if you have such history. It is theoretically possible that the proposed rTMS will increase the risk of seizures in individuals with no such history. In the unlikely event of a seizure, all members of the Brain Behavior Lab have been trained in CPR and first aid. The hospital will also send a team to the lab to assess you and determine if further evaluation is necessary. It is also possible that stimulation may affect your non-stroke hand. Other possible side effects could include headache, scalp discomfort, lightheadedness, tingling, spasms or twitching of facial muscles, discomfort from noise during treatment, hearing problems, and mania.

There may be other risks that have not yet been identified, and unexpected side effects that have not been previously observed may occur.

What are the Benefits to You of Participating in the Study

There is direct no benefit to you for participating in this study. It is hoped that additional information gained in this research study may be useful in the treatment of other patients with brain damage. You will be informed if any significant new findings develop during the course of the study that may affect your willingness to participate in this study.

Payments to Subjects

You will receive $35 for each clinic visit up to a total of $350 to offset your parking and or travel expenses incurred to participate in this study.

In the Event of an Injury

In the event you experience a serious side effect during this study, you should immediately contact Dr. Boyd at 604-822-7197. If it is after 5:00 p.m., a holiday or weekend, you should call Dr. Boyd at 778-329-8318. Signing this consent form in no way limits your legal rights against the sponsor, investigators, or anyone else. In case of a serious medical event resulting from this study, please report to an emergency room and inform them that you are participating in a research study and Lara Boyd (Principal Investigator) can be contacted for further information at 604-822-7392.

Confidentiality

Your confidentiality will be respected. No information that discloses your identity will be released or published without your specific consent to the disclosure. However, research records and medical records identifying you may be inspected in the presence of the Investigator or his or her designate by representatives of Health Canada and the UBC Clinical Research Ethics Board for

the purpose of monitoring the research. However, no records that identify you by name or initials will be allowed to leave the investigators' office.

To do this research, we need to collect health information that identifies you. We will collect information from activities described in the Procedures section of this form. If the results of this study are published or presented in public, information that identifies you will be removed. By signing this consent form, you are giving permission ("authorization") for UBC use and share your health information for the purposes of this research study. If you decide not to sign the form, you cannot be in the study.

Your study-related health information will be used at UBC by Dr. Boyd, and members of the research team. Your permission to use and disclose your health information remains in effect until the study is complete and the results are analyzed. After that time, information that personally identifies you will be removed from the study records.

Questions

You have read the information in this form. Dr. Boyd or their associates have answered your question(s) to your satisfaction. You know if you have any more questions after signing this you may contact Dr. Boyd or one of her associates at (604) 822-7197. If you have any questions about your rights as a research subject, you may call the Research Subject Information Line in the University of British Columbia Office of Research Services at (604) 822-8598.

You have a right to change your mind about allowing the research team to have access to your health information. If you want to cancel permission to use your health information, you may notify Dr Boyd in any way you wish. The mailing address is Lara Boyd, PT, PhD, University of British Columbia, T-325 – 2211 Wesbrook Mall, Vancouver, BC, V6T 2B5. If you cancel permission to use your health information, you will be withdrawn from the study. You may also verbally express your wishes to withdraw by telling a member of the research team or calling the lab at (604) 827-3369. The research team will stop collecting any additional information about you. The research team may use and share information that was gathered before they received your cancellation.

Consent

Dr. Boyd (or her associates) have given you information about this research study. They have explained what will be done and how long it will take. They explained any inconvenience, discomfort or risks that may be experienced during this study.

I freely and voluntarily consent to participate in this research study. I have read and understand the information in this form and have had an opportunity to ask questions and have them answered. **I will be given a signed and dated copy of the consent form to keep for my records.**

I have chosen not to receive a copy of this consent form _____ (Initial Here)

_____
Type/Print Subject's Name

_____ _____
Signature of Subject Date

_____
Type/Print Name of Witness

_____ _____
Signature of Witness Date

_____
Type/Print Name of Principle Investigator or their designate

_____ _____
Signature of Principle Investigator or their designate Date