

**EXPLORING THE NEURAL NETWORK UNDERLYING TASK-RELEVANCY
INFLUENCES ON MOVEMENT-RELATED GATING**

by

KATLYN ELIZABETH BROWN

BSc (Kinesiology), University of Waterloo, 2011

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF

MASTER OF SCIENCE

in

THE FACULTY OF GRADUATE STUDIES

(Rehabilitation Science)

THE UNIVERSITY OF BRITISH COLUMBIA

(Vancouver)

July 2013

© Katlyn Elizabeth Brown, 2013

ABSTRACT

Movement-related gating is influenced by task-relevancy manipulations, such that increased sensory information ascends to the cortex when information is relevant, but does not when it is irrelevant (1). Regardless of relevancy, during movement smaller cortical somatosensory responses are produced as compared to those evoked by similar stimulation at rest (1). These task-relevancy effects have specifically been documented during movement of the lower limb (1). Task-relevancy effects have been hypothesized to be controlled by the prefrontal cortex (PFC) based on this region's known role in selective attention, as well as filtering of distracting information at later stages of somatosensory processing (2). The purpose of the current study was first to verify task-relevancy influences on movement-related gating in the upper limb, and second to test the contribution of the PFC to these relevancy effects. Eleven healthy participants received median nerve stimulation at the left wrist during three conditions: rest, task-irrelevant movement, and task-relevant movement. The cortical responses to these median nerve stimulations were measured in the form of somatosensory evoked potentials (SEPs). Each of these three conditions was collected on a baseline day and on two separate days following either continuous theta burst (cTBS), which has a net inhibitory effect on cortical excitability, over the contralateral primary somatosensory cortex (S1) or the right dorsolateral prefrontal cortex (DLPFC). Results demonstrated a significant interaction effect between the stimulation site and the condition, with post-hoc tests revealing that following cTBS over S1 or DLPFC, relevancy based modulation of SEP amplitude was abolished. These results indicate that both S1 and DLPFC are integral to individual ability to facilitate relevant sensory information in order to complete a motor task.

PREFACE

This thesis contains a research experiment conducted by candidate, Katlyn E. Brown, under the supervision of Dr. Lara Boyd, with guidance from Dr. Richard Staines, Dr. Todd Handy, and Dr. Naznin Virji-Babul. The collection, analysis, and writing of the experiment were principally the work of the candidate. The supervisory committee provided direction, support, and critical feedback on the design of the study. This thesis will be submitted for publication as a multi-authored manuscript in peer-reviewed journals. Ethical review and approval for this thesis was performed by UBC Clinical Research Ethics Board (H12-01722).

TABLE OF CONTENTS

Abstract.....	ii
Preface	iii
Table of Contents.....	iv
List of Tables	vi
List of Figures.....	vii
List of Abbreviations	viii
Acknowledgements	ix
1.0 INTRODUCTION AND SPECIFIC AIMS	1
2.0 LITERATURE REVIEW	4
2.1 The Problem	4
2.2 Movement-Related Gating	4
2.3 Prefrontal Cortex	9
2.4 Connectivity.....	10
2.5 Continuous Theta Burst Stimulation	12
3.0 HYPOTHESES.....	14
4.0 METHODS	15
4.1 Participants	15
4.2 Experiment 1.....	15
4.2.1 Dependent Measures.....	16
4.2.2 Behavioural Task.....	17
4.3 Experiment 2.....	18
4.3.1 Intervention.....	18
4.3.2 Dependent Measures.....	20
4.4 Data Analysis.....	20
4.5 Statistics.....	21
4.5.1 Experiment 1.....	21
4.5.2 Experiment 2.....	21
5.0 RESULTS	22
5.1 Experiment 1.....	22
5.2 Experiment 2.....	22
5.2.1 Influence of cTBS on Movement-Related Gating.....	24

5.2.2 Influence of cTBS on Task-Relevancy Effects	24
6.0 DISCUSSION.....	25
6.1 Experiment 1.....	26
6.1.1 Neural Mechanisms Behind Movement-Related Gating.....	26
6.1.2 Neural Mechanisms of Task-Relevancy Effects on Movement-Related Gating	28
6.2 Experiment 2.....	32
6.2.1 Neural Mechanisms Underlying the Influence of DLPFC on Task- Relevancy Effects on Movement-Related Gating	33
6.2.2 Neural Mechanisms Underlying the Influence of S1 on Task- Relevancy Effects on Movement-Related Gating	36
6.3 Limitations.....	38
6.4 Significance	39
References	41
Appendices	47

LIST OF TABLES

Table 1: Summary of Inclusion and Exclusion Criteria	15
Table 2: Schedule for Experiments 1 and 2.....	15

LIST OF FIGURES

Figure 1: An SEP Trace.....	4
Figure 2: Corticospinal Influences on Primary Afferent Depolarization	6
Figure 3: Corticothalamic Connections from Prefrontal and Sensory Cortices	8
Figure 4: Neuroanatomic Connections between Prefrontal, Sensory, and Motor Cortices.....	12
Figure 5: N20-P26 Amplitudes From Experiment 1	22
Figure 6: SEP Traces From a Representative Subject	23
Figure 7: N20-P26 Amplitudes From Experiment 2	24
Figure 8: Descending Influences on Primary Afferent Depolarization.....	30
Figure 9: Attentional Influences on the Thalamic Reticular Nucleus and Sensory Thalamus	32
Figure 10: Prefrontal and Sensory Projections to the Thalamic Reticular Nucleus and Thalamus	35

LIST OF ABBREVIATIONS

AMT: Active motor threshold
APB: Abductor pollicis brevis
BOLD: Blood oxygenation level dependent
cTBS: Continuous theta burst stimulation
DCN: Dorsal column nuclei
DLPFC: Dorsolateral prefrontal cortex
EEG: electroencephalography
EMG: Electromyography
EPSP: Excitatory Post-Synaptic Potential
fMRI: Functional magnetic resonance imaging
GABA: Gamma-Aminobutyric acid
H-reflex: Hoffman reflex
IPSP: Inhibitory Post-Synaptic Potential
iTBS: Intermittent theta burst stimulation
M-wave: Motor wave
M1: Primary motor cortex
MEPs: Motor evoked potentials
MNI: Montreal Neurologic Institute
PAD: Primary afferent depolarization
PFC: Prefrontal cortex
PMd: Dorsal premotor cortex
S1: Primary somatosensory cortex
SENSE: Sensitivity encoding head coil
SEPs: Somatosensory evoked potentials
SMA: Supplementary motor area
TBS: Theta burst stimulation
TMS: Transcranial magnetic stimulation
TRN: Thalamic reticular nucleus
VPL: Ventral posterior lateral

ACKNOWLEDGEMENTS

I would like to thank Dr. Lara Boyd for a great two years, and for providing me with more opportunities than I could have imagined coming from an MSc. Your support and guidance is much appreciated.

In addition, I would like to thank Dr. Richard Staines for guiding me not only through my Master's, but through undergrad as well. I would not be the student I am today without your help.

Thank you to Dr. Todd Handy and Dr. Naznin Virji-Babul, you provided critical input at multiple stages along the way and this thesis would not have been the same without your invaluable input.

I am very grateful to everyone in the Brain Behaviour Lab for listening to many lab meeting presentations, for help during collection, and making a room with no windows tolerable over the last two years. Special thanks to Jen Ferris for all of her help with data collection and analysis.

Finally, to my friends and family, I thank you for the endless years of support.

1.0 INTRODUCTION AND SPECIFIC AIMS

The overall objective of this thesis is to determine whether the prefrontal cortex, through the allocation of attentional resources, is responsible for task-relevancy effects on movement-related gating.

In healthy individuals, sensory information from the periphery is filtered as it ascends to the cortex; the most important, or relevant, information causes the greatest response in the primary somatosensory cortex (S1) (1,3). This ability to extract relevant sensory information despite an overwhelming barrage of concurrent sensory feedback enables successful interaction with one's environment. A specific form of gating, movement related gating, involves attenuated somatosensory responses, as measured by the size of early somatosensory evoked potential (SEP) components (N20-P26), to stimuli during movement (4). Past work has shown that as compared to rest, voluntary movement results in smaller sensory responses (e.g., smaller N20-P26s); however, when sensory feedback is essential for task performance, greater activity is seen in S1 (e.g., larger N20-P26s) (1,3). Though this general pattern has been consistently shown across studies (5), the neural network that underpins this pattern of brain excitability has yet to be elucidated.

The prefrontal cortex (PFC) has been hypothesized to be the cortical area largely responsible for the task-relevancy effects seen in movement-based gating patterns. Other work has established the PFC as influencing gating at rest (1,6), where it has been commonly implicated in affecting later cortical potentials (e.g., P100) indicative of secondary somatosensory processing, such as the integration of information between modalities (2). In support of prefrontal influences on sensory processing, functional magnetic resonance imaging (fMRI) studies have shown that attentional manipulations

that focus on particular stimuli increase activity in contralateral S1 and dorsolateral prefrontal cortex (DLPFC), as measured by blood oxygenation level-dependent (BOLD) changes (3). Logically, it appears that the PFC also influences sensory gating during movement; however, this theory has yet to be directly tested.

The somatosensory system is as an integral component of motor learning (7). Disruption of somatosensation impairs performance on implicit motor learning paradigms; specifically, increased proprioceptive loss is associated with less improvement in performance on an implicit motor sequence-learning paradigm (7). Importantly, if the PFC filters irrelevant information and allows for facilitation of relevant information to the somatosensory system, the neural network responsible for task-relevancy effects on movement-related gating may influence motor learning. In order to apply this hypothesis to motor learning paradigms, the intricacies of this prefrontal task-relevancy network must be established.

Theta burst stimulation (TBS) is a form of noninvasive brain stimulation that can alter cortical excitability. Continuous theta burst stimulation (cTBS) has an inhibitory effect on the area over which the stimulation is applied, whereas intermittent TBS (iTBS) has an excitatory effect (8). The duration of these changes in cortical excitability is approximately 40 minutes (8). Transiently inhibiting the DLPFC using cTBS allows for direct testing of the role of the DLPFC in modulating the attentional effects on the movement-related gating paradigm.

Taken together, past work investigating sensory gating effects and data demonstrating regional contributions to gating suggest a role for the PFC in movement-related sensory gating. The present thesis is designed to assess whether the PFC is

responsible for task-relevancy based influences on movement-related gating and will consider two specific aims, which will be tested in two experiments.

Specific Aim 1: To replicate, in the upper limb of healthy individuals, the task-relevancy effects on movement-related gating, which have previously only been shown in the lower limb.

Neuroelectrical activity (electroencephalography (EEG)) resulting in median nerve stimulation will be used to probe the somatosensory system. Specifically, SEP N20-P26 amplitudes will be measured at rest, and during two movement conditions with differing task-relevancy demands. This will allow for examination of movement-related gating patterns in the arm, as well as task-relevancy influences on these gating patterns.

Specific Aim 2: To understand the contributions of S1 and DLPFC to task-relevancy effects on movement-related gating.

The measures taken in experiment one will provide a baseline for experiment two. The second experiment will assess SEP amplitude in the same conditions as experiment one following transient inhibition over S1 or DLPFC to parse out the unique contributions from these two cortical areas.

2.0 LITERATURE REVIEW

2.1 The Problem

The determination of underlying neural networks is essential to furthering understanding of cortical functioning. Elucidating the role of the DLPFC in movement-related gating will allow for investigation into compensations made within this network following damage or the interplay between the DLPFC and S1 after stroke.

2.2 Movement-Related Gating

Movement-related gating occurs during movement of extremities and results in decreased transmission of somatosensory information to the cortex (5). This phenomenon was first seen in 1964 when Giblin observed that the SEPs resulting from median nerve stimulation had lower amplitudes when individuals were voluntarily moving their fingers (9). Multiple studies since then have shown that this pattern holds for both active (volitional) and passive (non-volitional) movements (10-13). Specifically, as measured by EEG, the early components of the SEP (N20, P26) have diminished amplitude with movement of the stimulated arm. In contrast, the long latency potentials (P100, N140) have increased amplitude with similar movement (14).

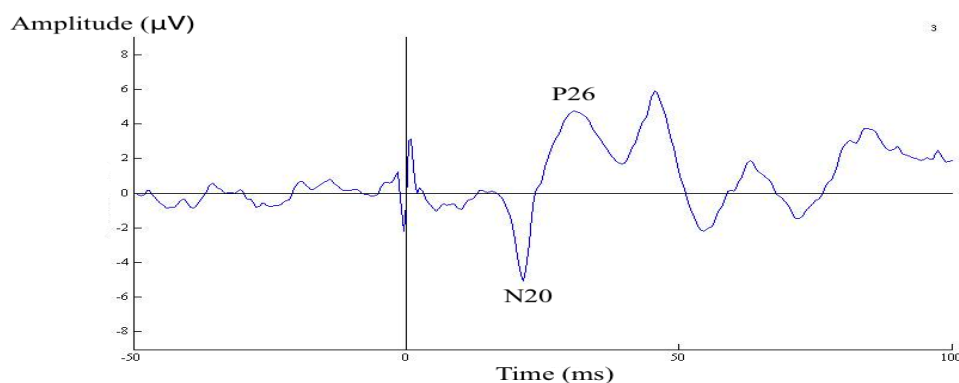


Figure 1: An SEP Trace. N20-P26 components representing the arrival of sensory information at Brodmann areas 3b and 1, respectively, are labeled. (Data are from the CP4 electrode).

Movement-related gating is the result of peripheral and central mechanisms. From the periphery to the cortex, somatosensory information is transmitted through two levels of nuclei: the dorsal column nuclei (DCN) and the ventral posterior lateral (VPL) nucleus (caudal division) of the thalamus, as well as having synapses in the spinal cord itself (5,15,16). In a cat model, transmission of afferent signals through the DCN is diminished by approximately 20-39% leading up to, as well as during movement (15,16). This suppression is thought to be of central origin as reduced signals can be seen in the DCN prior to the onset of electromyography (EMG) (15,17). As sensory information ascends to the VPL further gating is seen before and during movement with approximately 47% of the information being filtered out (17). This level of gating is attributed to peripheral gating mechanisms as the modulation is seen *following* EMG onset, whereas cortical influences typically occur *prior* to movement (16). Evidence is also present in humans that peripheral stimulation results in a marked decrease in sensory transmission both prior to and during movement, suggesting both peripheral and central contributions to gating (4,18). Cortically, this can be documented by examining the early component of the SEP (N20-P26), representing the arrival of somatosensory feedback to S1; this potential is attenuated during movement (18,19). As mentioned above, the early latency potentials of the SEP (N20, P26) are decreased with movement, whereas the long latency potentials (P100, N140) are facilitated (14). As information ascends to the cortex, increased gating takes place. Studies have shown a decrease in amplitude at the cortex by approximately 63% (20).

The primary motor cortex (M1) has been implicated in cortically driven gating. M1 contains neurons, which are active before the onset of movement suggesting a cortical

origin for gating (21,22). M1 was shown by Jiang et al (1990a) to directly modulate information for skin areas that would be affected by movement (21). Given these findings, neuroanatomic connections were examined to determine the potential neural mechanisms by which M1 exerts its effects.

The motor cortex is the site of origin for the corticospinal tract, which descends and terminates in the dorsal horn of the spinal cord (23). Therefore, M1 may exert its effects via primary afferent depolarization (PAD), which alters sensory transmission in primary afferent terminals (Figure 2) (24). PAD of 1a afferent fibres is inhibited by the activity of the red nucleus, bulbar reticular formation, and the nucleus raphe magnus, and the motor cortex, which is of primary importance in relation to movement-related gating (25).

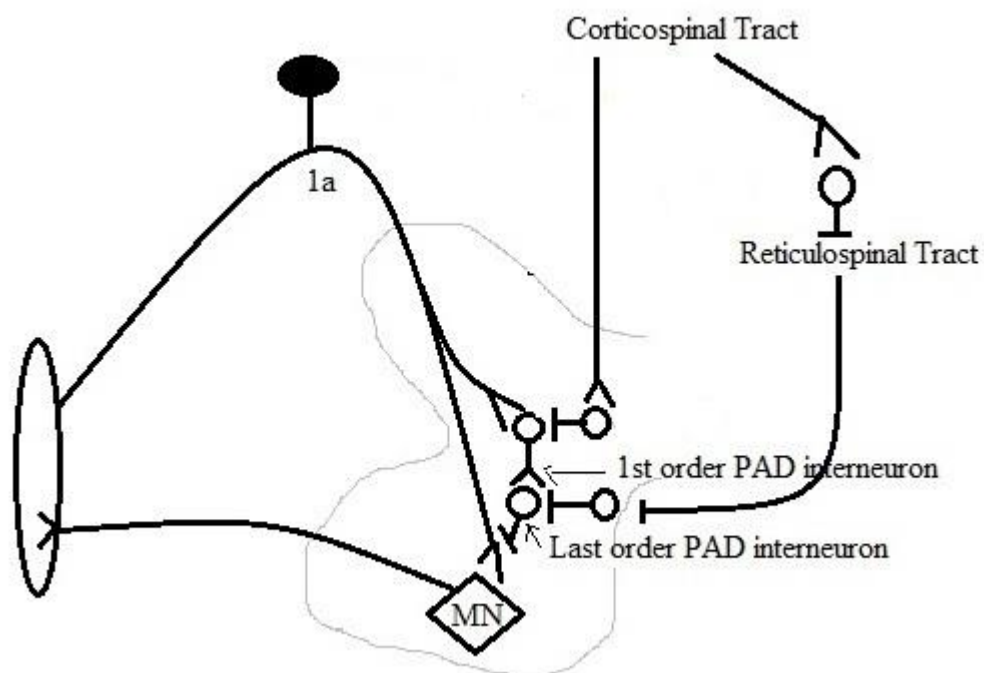


Figure 2: Corticospinal tract contributions to PAD in a cat model. Straight lines indicate inhibition while excitatory synapses are Y-shaped. 1st order PAD interneurons receive inhibition from the corticospinal tract. The reticulospinal tract inhibits the last order PAD interneuron; however, this level of inhibition can be altered by the corticospinal tract (26).

In the dorsal column nuclei, similar to the spinal cord, the effect on somatosensory input is thought to largely originate in the motor cortex (23). The motor cortex has its own projections that can control afferent input, and can also influence incoming afferent information through various descending systems, such as the red nucleus and superior colliculus (23). At this level, presynaptic inhibition initiated cortically by M1 is thought to be the major modulator of somatosensory input (23).

At the thalamic level, the motor cortex also has major contributions to sensory gating (23). M1 is ideally connected to influence thalamic relay nuclei via the thalamic reticular nucleus (TRN) (27). Projections from layer V1 of the motor cortex extend to the TRN (27-29). The TRN, which surrounds the thalamic sensory relay nuclei, is composed of GABAergic cells and suppresses activity to S1 (27). By exciting the TRN, inhibition of the VPL can resultantly inhibit transmission of information to S1. Through systems of interneurons, the TRN is also able to disinhibit or facilitate sensory transmission to the cortex (27).

Attentional mechanisms have also been shown to affect gating levels at rest and during movements. Attending to specific peripheral stimuli while ignoring other stimuli leads to a facilitation of the relevant information in the sensory domain, as well as in other modalities (1-3). This cortical influence can impact both early and late components of somatosensory processing; however, the exact mechanisms behind this differential impact have yet to be determined. As can be seen in Figure 3, the PFC, which is important in attentional processes, has anatomic connections to the TRN, which are interspersed with connections from the sensory and motor cortices. The potential role of the PFC in movement-related gating will be discussed below.

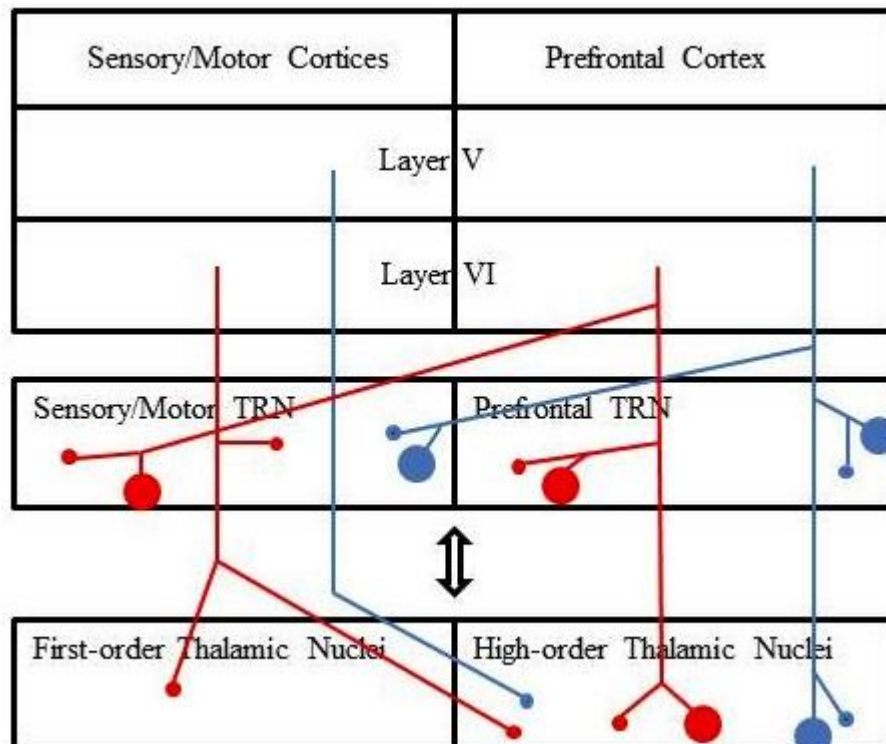


Figure 3: Corticothalamic projections issued by prefrontal and sensory/motor cortices. Most of the sensorimotor projections arise from layer V1 and terminate in the thalamus as small boutons, as well as sending collateral branches to the TRN. Connections arising from layer V project to higher order sensory relay nuclei, but do not have collaterals to the TRN. In contrast, the PFC has corticothalamic projections from layer V terminating as both large and small boutons in high order nucleus as well as the TRN.

Movement-related gating, therefore, is influenced by mechanisms resulting directly from environmental stimuli, as well as by cortical processing. Such gating has a protective effect in individuals and prevents an overload of somatosensory information from reaching cortical levels. Impairment to this system, resulting from nervous system damage could be detrimental to daily life if individuals cannot filter out distracting information. Alternately, after neuropathology it is also possible that relevant sensory information could be inappropriately filtered. Exploration into the cortically driven modulation of gating is required to understand whether this system can be differentially regulated in order to compensate for damage to underlying neural structures. Logically,

these data could lead to the development of new therapies that compensate for ineffective gating after neural damage.

2.3 Prefrontal Cortex

Neuroanatomically, the DLPFC is the cortical area largely responsible for selective attention. Studies show activity in the DLPFC during attention-based tasks, and following PFC damage attention deficits are common (6,30). PFC damage may lead to an inability to filter out irrelevant incoming sensory stimuli, impairing the ability for one to attend to specific sensory stimuli in the presence of distractors (31). To examine this network in the undamaged brain, a recent study investigated the effect of cTBS over DLPFC on a tactile-attention task (2). Individuals received tactile stimulation of differing sizes to their second and fifth digits while performing a task that involved filtering out specific sized stimuli to one digit (2). Cortical potentials (P100s) that are typically inhibited when stimuli are irrelevant were not attenuated following cTBS as compared to a control group who received sham stimulation, suggesting that the DLPFC is an integral part of somatosensory-based attentional networks (2). Further supporting a role for the PFC in sensory processing, a functional magnetic resonance imaging (fMRI) study showed that when healthy subjects were instructed to attend only to relevant tactile information, increased cortical activity was noted in contralateral S1, while activation decreased in ipsilateral S1 (3). When the tactile stimuli were irrelevant, increased activity in S1 was not evident. Moreover, similar task-related changes in DLPFC activity were also noted, suggesting a prefrontal cortical gating mechanism. During movement conditions, the DLPFC has also been suggested to be responsible for relevancy-based filtering of information (3).

In a movement-based experiment probing the proprioceptive system, task-relevancy has been shown to influence somatosensory information processing and sensory gating (1). This study contained three major components: a rest condition, a task-irrelevant movement condition, and a task-relevant movement condition (1). Nerve stimulation in the rest condition produced the largest responses indexed by SEPs (N20-P26 component) in S1. Both a task-irrelevant condition in which participants' feet were moved through a series of plantar flexion and dorsiflexion movements with no focus on proprioceptive feedback, and a task-relevant condition in which participants were instructed to attend to the position of their passively moved foot and match that position with their other foot, produced lower early SEP components than the rest condition (1). Specifically, the components corresponding to S1 activity were altered based on these attentional manipulations (1). Taken together, this work suggests that the DLPFC has the ability to influence sensory gating at rest and during movement at early stages of somatosensory processing.

2.4 Connectivity

The diffuse projections of the DLPFC offer numerous possibilities for how task-relevancy effects on somatosensory gating occur. For example, in a cat model, the DLPFC suppresses the thalamic input to S1 (32). Thalamocortical projections allow individuals to selectively focus their attention and inhibit information that is determined to be irrelevant (32). Damage to the DLPFC, therefore, leads to the enhancement of SEPs, or evoked potentials linked to other modalities, thus offering a possible explanation for the absence of somatosensory gating following prefrontal lesions (32). Enhanced SEPs at rest following prefrontal damage suggests a tonic inhibition (4); however, the N20 component

is not enhanced in individuals with prefrontal lesions when compared to controls.

Alternatively, literature on selective attention suggests more cortical control over the information reaching S1 (2,5,34).

Connections that may facilitate such cortically driven modulation are also present between the DLPFC and the somatosensory cortex, as inhibitory connections exist between these two areas (6). Areas 1 and 2 in the primary somatosensory cortex bidirectionally connect to areas 4 and 6 (6). Areas 5 and 7, which are somatosensory association areas, have bidirectional connections to the DLPFC, as well as to the supplementary motor area (SMA) (6). Areas 1 and 2 have reciprocal interconnections with areas 5 and 7, meaning that pathways between the DLPFC exist to various areas of the somatosensory cortex that generate SEP components, except for area 3b (6). These connections have the potential to be responsible for somatosensory gating. Specifically, the enhancement seen at P26 following prefrontal lesions is thought to be the result of impaired inhibitory pathways from the DLPFC to S1 (6).

The DLPFC also has projections, excitatory in nature, to the TRN (3). The TRN contains distinct systems for somatosensory, visual, and auditory information, with the somatosensory section maintaining a topographic representation throughout (27). The DLPFC, by exciting the TRN, inhibits the sensory relay nuclei in the thalamus, which may lead to the gating of irrelevant sensory information (27). In opposition, the DLPFC-TRN pathway could also alter its activity in order to facilitate the transmission of relevant information to the cortex by disinhibiting the transmission through the thalamic relay nuclei (27). Due to the diffuse projections from the DLPFC directly, and indirectly to S1,

the DLPFC is in a prime position to modulate gating patterns within the central nervous system.

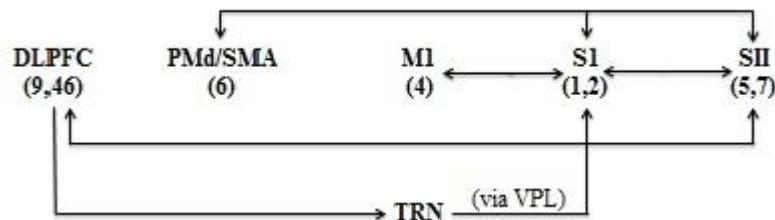


Figure 4: Neuroanatomical connections between DLPFC and S1. DLPFC, indirectly through the thalamus or secondary somatosensory connections, connects to S1.

In the auditory system, the TRN is an integral part of the most recently published underlying model (33). When gating out a second auditory stimuli, it is hypothesized that the PFC, as well as other cortical areas, project back to the TRN following the initial stimuli processing; alteration of TRN excitability leads to a diminished response to the second stimuli (33). As similar gating processes are seen in the sensory and auditory domains it is feasible that a similar process may be at work in the somatosensory system.

2.5 Continuous Theta Burst Stimulation

Transcranial magnetic stimulation (TMS), through electromagnetic induction, allows for noninvasive activation of neurons local to the stimulation. Specifically, in this thesis the technique of cTBS was implemented in order to transiently inhibit specific cortical regions (S1 and DLPFC). These inhibitory effects have been shown to last for a period of approximately 40 minutes (8). cTBS consists of a train of 600 pulses delivered at 50 Hz, lasting 40 seconds block (8). cTBS was first introduced in the motor cortex and was successful in reducing the amplitude of motor evoked potentials (MEPs) (8). cTBS has also been successfully administered to other cortical areas including S1, DLPFC, and dorsal premotor cortex (PMd) (34). Of interest for the current study is stimulation over

the primary somatosensory cortex and the DLPFC, both of which have successfully been inhibited via cTBS in prior work (2,7,34).

3.0 HYPOTHESES

Specific Aim 1: Replication in the upper limb

Hypothesis 1: As has been seen in the lower limb, the N20-P26 amplitudes will be largest in the rest condition and diminished with movement in the task-irrelevant condition.

Facilitation above gated levels will be noted when attention is directed towards the proprioceptive feedback from the passively moved arm. This follows what has been found in the lower limb (1). As proprioceptive information and afferent feedback resulting from nerve stimulation in both the lower and upper limb travels through the dorsal column-medial lemniscal pathway, it is unlikely that a discrepancy between gating in the lower versus upper extremities will be noted.

Specific Aim 2: Effect of brain stimulation over DLPFC and S1

Hypothesis 2: cTBS over DLPFC will cause a reduction in the attentional effects associated with movement-related gating; both the task relevant and task irrelevant movement conditions will produce N20-P26 amplitudes significantly smaller than a resting condition. There will be no difference based on relevancy. cTBS over S1 will not alter task-relevancy effects on movement related gating; however, the N20-P26 amplitude in each condition will be diminished as compared to the amplitudes seen without stimulation.

4.0 METHODS

4.1 Participants

Eleven (5 males, 6 females) healthy right-handed individuals (26 ± 5 years) participated in both experiments. Written consent in accordance with the University of British Columbia Ethical Review Board was obtained prior to participation and individuals were screened for contraindications to TMS or MRI procedures.

Inclusion Criteria	Exclusion Criteria
Ages 19-35	Family history of epilepsy or history of seizures
	Psychiatric diagnosis; neurodegenerative disorder; substance abuse or surgery; neurological or muscular deficits that affect vision, oculomotor, or manual control
	Presence of implanted electrical devices; pregnancy or choice of pregnancy

Table 1: Summary of Inclusion and Exclusion Criteria

Briefly, participants were excluded if they had any neurodegenerative or musculoskeletal disorders, as well as a history of epilepsy or head trauma. Each participant completed four sessions: an MRI, a baseline measurement session, a DLPFC stimulation session, and an S1 stimulation session.

	Day	Purpose	Tasks	Dependent Measures
Experiment 1	1	MRI	n/a	n/a
	2	Baseline	Rest, TI, TR	SEP amplitudes
Experiment 2	3	cTBS S1	Rest, TI, TR	SEP amplitudes
	4	cTBS DLPFC	Rest, TI, TR	SEP amplitudes

Table 2: Schedule for Experiments 1 and 2. The order of days 3 and 4 were randomized for each participant. TI: Task-irrelevant, TR: Task-relevant

4.2 Experiment 1 – Replication in the Upper Limb

The impact of attentional manipulations on movement-related gating in the upper limb was explored in eleven individuals. To facilitate stereotaxic guidance of non-

invasive brain stimulation each participant first underwent a T1-weighted anatomic MRI scan at the UBC 3T Research MRI Centre. Following the MRI, participants completed the experimental protocol in the Brain Behaviour Laboratory at the University of British Columbia.

4.2.1 Dependent Measures

To assess the arrival of information in S1 (Brodmann areas 3b and 1), EEG was used to examine the N20-P26 components of SEPs resulting from median nerve stimulation. A bar electrode was placed on the left wrist, just above the median nerve. A square wave pulse (0.5 ms) was delivered (Grass SD9 Stimulator with SIU-V Isolation Unit, West Warwick, RI, USA) at an intensity of motor threshold (the intensity required to evoke a just visible twitch). The interstimulus interval was randomly generated between 500 and 1000 ms to ensure the stimulations were not predictable. 110 stimulations were delivered in each condition and an average trace was produced in the analysis program. To ensure changes in SEP amplitude were the direct result of task manipulations, motor wave (M-wave) amplitude was monitored. M-wave amplitude was monitored using Ag-Cl electrodes placed over the muscle belly of the left abductor pollicis brevis (APB) muscle. As M-waves result from efferent nerve stimulation, this monitoring ensures a constant number of stimulated fibres. EEG was recorded from electrodes C4 and CP4 (contralateral sensorimotor regions) throughout each condition with a TMS compatible cap referenced to AFz (2000 Hz sampling rate) (NeuroPrax; Neuroconn, Ilmenau, Germany). Channel impedances were $< 5 \text{ k}\Omega$.

4.2.2 Behavioural Task

To ensure random sequences of movement, a custom LabView program (LabVIEW 8.5; National Instruments, Austin, Texas, USA) was used to direct the experimenter during passive movements. The experimenter followed a sinusoidal trace produced on the screen, which translated into wrist flexion and extension for participants. Participants sat in an upright chair, with elbows bent at 90 degrees. Their hands were secured in a custom-made wrist movement device allowing for near-frictionless flexion and extension in the horizontal plane. Eyes were closed for the duration of the task to emphasize proprioceptive feedback. Each movement condition involved the experimenter passively moving the non-dominant hand. The task of the participant varied based on conditions, which are outlined below.

The SEPs were taken in three main conditions, with the order randomized for each participant:

Resting Condition

A rest condition in which the participant sat with his or her hands in the device and median nerve stimulation was delivered to the left wrist. The rest condition was included to establish a baseline SEP amplitude to which gated levels could be compared.

Passive Movement Condition

A task-irrelevant condition in which the participant's non-dominant hand was moved through a series of motions while median nerve stimulation was delivered at the left wrist. This condition was included to index typical movement-related gating. The passive movement condition, in comparison to the rest condition, was expected to produce an attenuated response in S1.

Active Movement Condition

A task-relevant condition in which the participants matched the movement of the non-dominant hand with movement of the dominant hand. Attention was therefore directed to the proprioceptive feedback in the non-dominant hand in order to match with accuracy. The participant's non-dominant hand was passively moved for 7 seconds, before being placed back in a neutral position. Median nerve stimulation was delivered during the passive movement only. Once the non-dominant hand was resting in neutral, the participant started moving the dominant hand. This condition, when compared to both resting conditions and passive movement conditions allows for the testing of replication of patterns in the lower limb; resting median nerve stimulation was expected to produce the largest N20-P26 amplitudes followed by median nerve stimulation during task-relevant movement conditions, with task-irrelevant conditions producing the smallest N20-P26 amplitudes in response to median nerve stimulation.

4.3 Experiment 2 – Effect of Brain Stimulation

The impact of cTBS over DLPFC and S1 on task-relevancy manipulations to a proprioceptive-based movement task in the upper limb was tested in the same eleven individuals as participated in experiment one. Each participant received both location of stimulation in separate sessions one week apart.

4.3.1 Intervention

cTBS over DLPFC and S1 was delivered using a Magstim SuperRapid stimulator with a cooled 7 cm figure-of-eight coil (Magstim Company Ltd., Wales, UK). For the duration of the TMS portion of the experiment, participants were seated in a semi-reclined dental chair with their arms supported. APB EMG activity was recorded during the

median nerve stimulation, and was also targeted with the TMS. Active motor threshold (AMT) for APB in M1 was obtained. AMT is the stimulator output at which an MEP >200 μ V is elicited on 5 out of 10 trials while participants maintain an APB contraction of 20% of their maximal force, as measured by surface EMG (35). cTBS consists of a series of bursts of three pulses 20 ms apart, repeated every 200 ms for 40 s (600 total pulses) at 80% of AMT for APB (8). When applied over DLPFC, the coil was held at a 90° angle to the mid-sagittal line (2,34). When applied over S1, the coil was held at a 45° angle to the mid-sagittal line with the handle in a posterior lateral orientation (7).

Prior to completion of any TMS measures, a high-resolution anatomical MRI was collected for each participant (TR = 12.4 ms, TE = 5.4 ms, flip angle α = 35°, FOV = 256 mm, 170 slices, 1 mm thickness) at the UBC MRI Research Centre on a Phillips Achieva 3.0T whole body MRI scanner (Phillips Healthcare, Andover, MD) using a sensitivity encoding head coil (SENSE). The images acquired in this session were imported into BrainSight (Rogue Research Inc., Montreal, QC), a TMS neuronavigation software, in order to register the coil in stereotaxic space. This registration enabled insertion of the coordinates for DLPFC into the software and ensured the coil was placed over these precise coordinates. In order to locate S1, the coil was marked on Brainsight as being 2 cm posterior and 1 cm lateral to the APB hotspot. To ensure stimulation of M1 was not taking place, single pulses were delivered over this location to confirm no EMG activity was recorded. For the DLPFC, coordinates from past functional MRI work were used (MNI: x, y, z = 40, 21, 27) (36). In order to convert the images into MNI space, the anterior and posterior commissures were identified in each individual's MRI, and bounding boxes were set around the cortex. Using Brainsight software, the images were

then converted into MNI space based on the previously mentioned identification. The two stimulation sites were delivered in random order between participants (as assigned by a random generation computer program). The sessions occurred a week apart in order to ensure that the first part of the experiment did not interfere with the second one (37). All stimulation parameters were within published safety standards (38).

4.3.2 Dependent Measures

The same conditions and procedures as were followed in experiment one were repeated after cTBS had been applied in the second experiment. As the same individuals participated in both experiments, the data collected in the first experiment served as a baseline measure. The participants began the session with cTBS over one of the two locations and then completed the conditions that were outlined in experiment one. EEG was collected throughout the conditions, but not during the application of TMS. The same proprioceptive task was used. The order of these conditions was randomized.

4.4 Data Analysis

EEGlab (Swartz Center for Computational Neuroscience, University of California San Diego, San Diego, California, USA) software was used to analyze the SEP data. SEPs were extracted via epochs time-locked to median nerve stimulation (-100 ms to 300 ms). Inspection was used to manually reject noisy trials and the remaining epochs were used to produce an average trace. Peak amplitudes of the N20 and P26 components of the SEPs were derived from this average trace. The peak-to-peak value (P26 amplitude – N20 amplitude) was the dependent measure for statistical testing.

4.5 Statistics

4.5.1 Experiment 1

A 1x3 (Day (baseline) x Condition (rest, task irrelevant, task relevant)) repeated measures ANOVA (dependent variable: N20-P26 amplitude) was used to test hypothesis 1. As movement-related gating has been well documented in the upper limb, the main difference in amplitude to be examined was between the task-irrelevant and task-relevant movement conditions. This difference was tested using a follow-up t-test (two-tailed) to elucidate a potential influence of task-relevancy on gating.

4.5.2 Experiment 2

A 3x3 (Stimulation site (none, DLPFC, S1) x Condition (rest, task irrelevant, task relevant)) repeated measures ANOVA (dependent variable: N20-P26 amplitude) was used to evaluate the interaction between conditions and stimulation sites. An interaction effect would indicate that the conditions are being influenced differently based on the stimulation day, which was hypothesized to be the case. If an interaction effect was present, post-hoc t-tests were used to determine the locus of the interaction. Specifically, based on the hypothesis, DLPFC stimulation was expected to reduce the task-relevancy increase seen between passive and active conditions, whereas baseline and S1 stimulation days were not expected to have this effect.

5.0 RESULTS

5.1 Experiment 1

A 1x3 (Day x Condition) repeated measures ANOVA (dependent variable: N20-P26 amplitude) revealed a significant effect of condition ($F_{(2,20)}=15.883$, $p<0.000074$). Follow-up paired t-tests reveal a significant difference between the task relevant and task irrelevant movement conditions ($t_{(10)}=-2.281$, $p=0.046$). The N20-P26 component was of greater amplitude in task relevant conditions, than in task irrelevant conditions. It should be noted that this follow-up t-test was of primary interest as it directly tests our hypothesis regarding the relevancy effects on movement-related gating. The general pattern of movement related gating, with smaller SEPs being produced during movement than at rest, has been well documented in the literature; therefore, confirming this was secondary ($t_{(10)}=5.199$, $p=0.000402$).

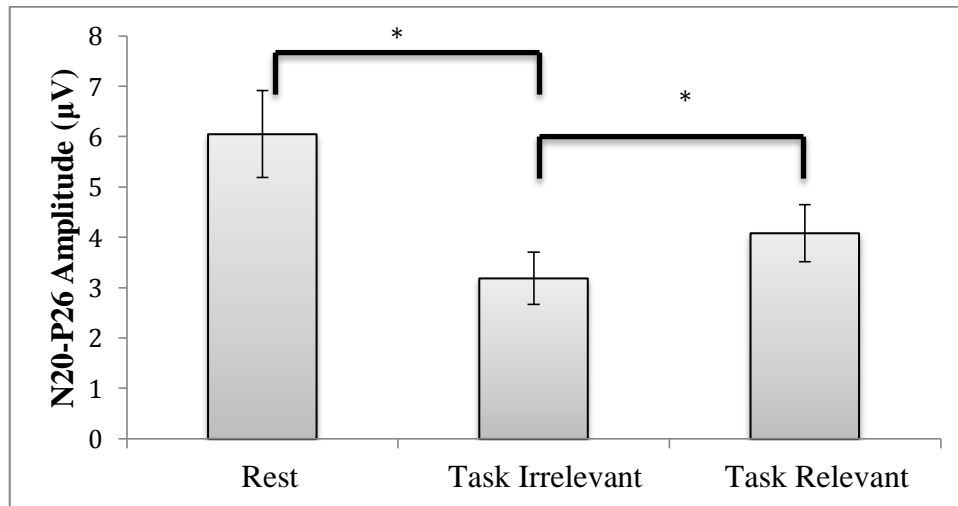


Figure 5: N20-P26 amplitudes from Experiment 1. CP4 electrode.

5.2 Experiment 2

The results from experiment one were used as a baseline measure for the second experiment as they examine the influence of task-relevancy in movement related gating prior to any cortical stimulation. A repeated measures ANOVA (dependent variable: N20-

P26 amplitude) revealed a significant interaction effect between condition (rest, task-irrelevant, task-relevant) and site of stimulation (baseline, DLPFC, S1) ($F_{(4,36)}=2.847$, $p=0.038$). In order to address whether the stimulation was affecting movement related gating itself, or the task-relevancy effects on it, follow-up t-tests were conducted.

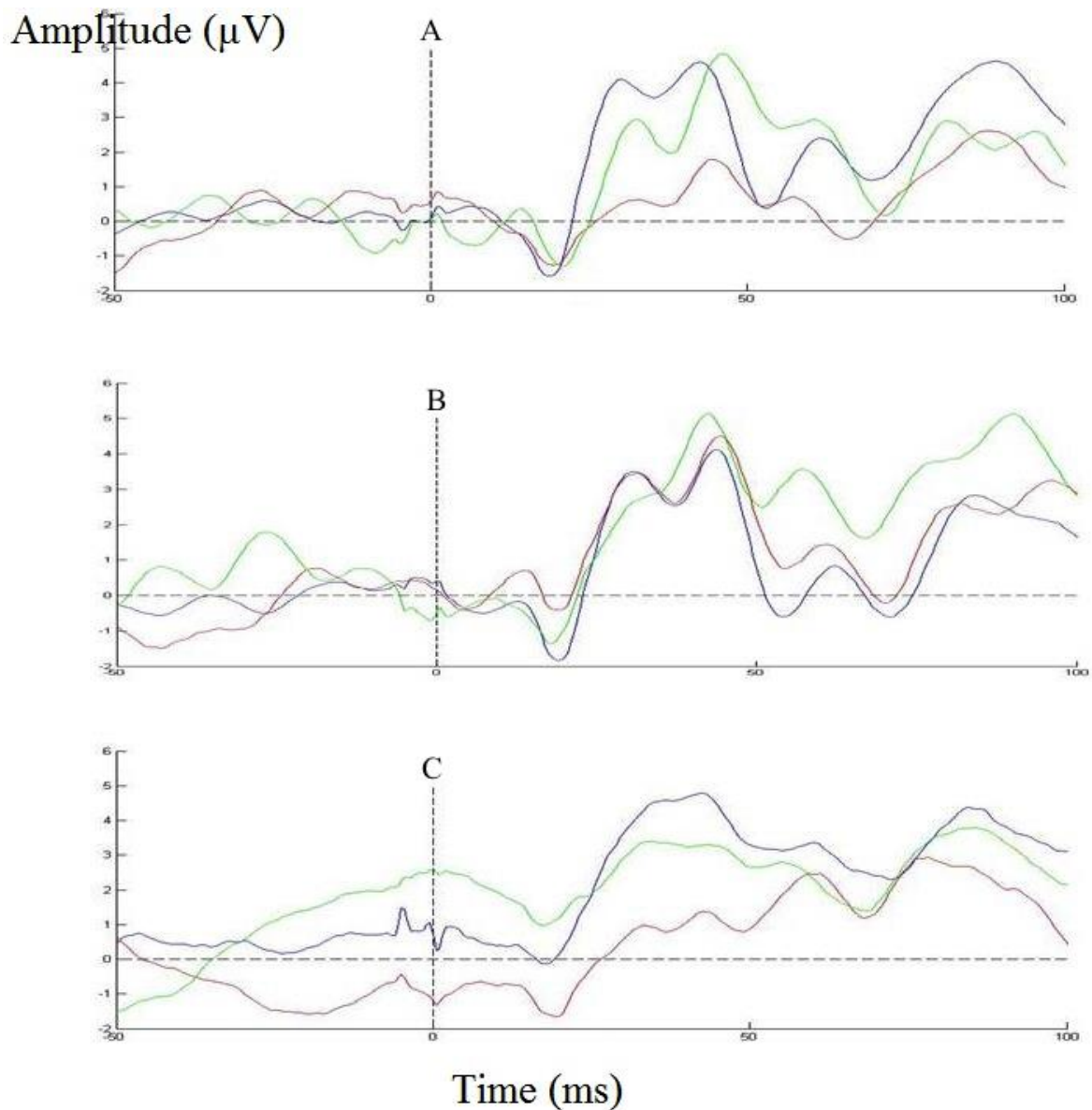


Figure 6: SEP traces from a representative subject (CP4 electrode). Blue traces represent the rest condition, red traces represent the task-irrelevant condition, and green traces represent the task-relevant condition. A is the SEP traces from Day 1, B is the SEP traces following cTBS over S1, and C is the SEP traces following cTBS over DLPFC.

5.2.1 Influence of cTBS on Movement-Related Gating

Following cTBS over S1, a difference between the movement conditions and rest remained ($t_{(10)}=2.411$, $p=0.037$). Also, following cTBS over DLPFC, this movement-based difference remained ($t_{(10)}=2.308$, $p=0.044$). In both cases, resting N20-P26 amplitudes were greater than the amplitudes in movement conditions. Following a Bonferroni correction, these were trending towards significance (level $p=0.025$).

5.2.2 Influence of cTBS on Task-Relevancy Effects

In order to parse out whether there was a direct influence of stimulation on task-relevancy effects on gating, follow-up t-tests were performed to compare N20-P26 amplitude in the task-relevant and task-irrelevant conditions. Following stimulation over S1 or DLPFC, there is no difference between relevancy conditions ($t_{(10)}=1.563$, $p=0.149$, $t_{(10)}=1.300$, $p=0.223$, respectively).

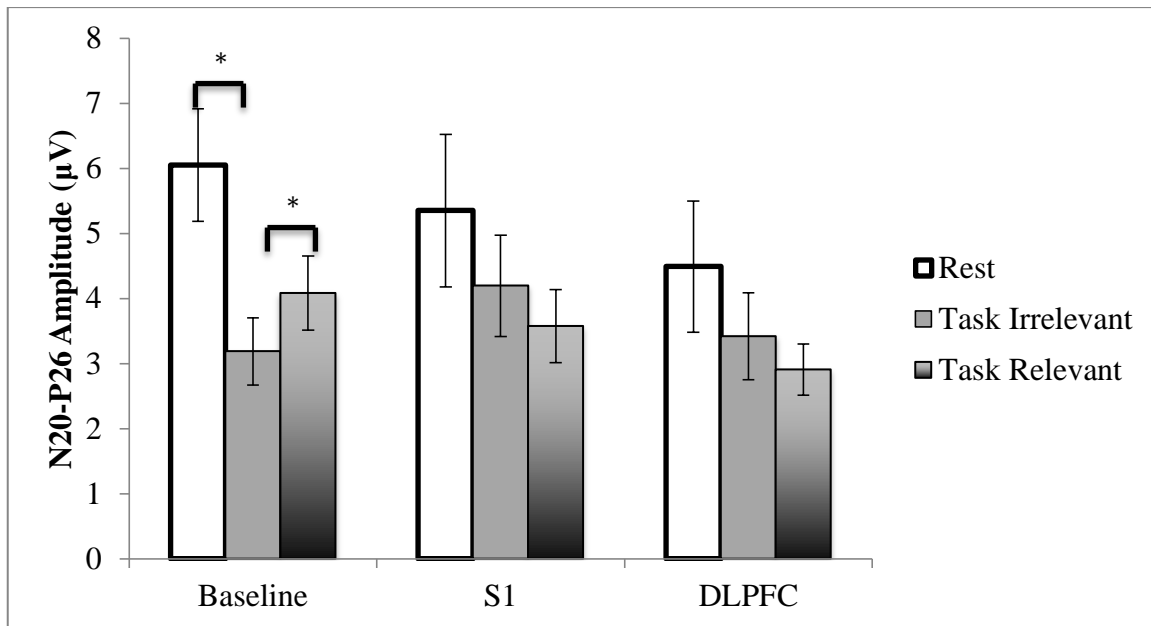


Figure 7: N20-P26 amplitudes from Experiment 2. CP4 electrode.

6.0 DISCUSSION

The present results demonstrate that task-relevancy manipulations can influence levels of movement-related gating in the upper limb. Further, the results implicate both the DLPFC and S1 as being integral to task-relevancy based facilitation of sensory information. As hypothesized, median nerve stimulation delivered over the left wrist of the young, healthy individuals in the current study produced the largest cortical responses in S1, as measured by the N20-P26 component of the SEP, when the participants were not moving. Passive movement of the left wrist diminished the amplitude of these responses; however, if the sensory feedback from the movement was task-relevant, cortical sensory responses were enhanced above gated levels. Following cTBS over either right DLPFC or S1 to induce short-lasting inhibition, movement-related gating was still shown, but task-relevancy based facilitatory effects were not. Particularly, while the depression from resting amplitudes to the amplitudes seen with movement remained, when individuals attended to the sensory feedback from movement to perform the task, increased sensory information did not reach the cortex.

Task-relevancy based effects on movement-related gating had been hypothesized to occur following transient inhibition of the DLPFC, due largely to its role in selective attention and sensory processing. Therefore, our results support this hypothesis; following cTBS, which induces transient inhibition of the DLPFC, the task-relevancy based facilitation seen in our baseline measures was impaired. This is indicative of prefrontal control over selective sensory processing during movement-related gating.

In contrast to my hypothesis the application of cTBS over S1 induced the same result as cTBS over the DLPFC. The task-relevancy based modulation of incoming

sensory information during movement was impaired following transient inhibition of S1. Exclusively, this would suggest that S1 has the ability to modulate incoming sensory information based on relevancy to task performance. Together, with the DLPFC results it is likely that *both* the DLPFC and S1 are essential to efficient task-relevancy based modulation of incoming sensory information during movement. Potential mechanisms for these results will be examined below.

6.1 Experiment 1

The results from experiment one indicate that task-relevancy effects on movement-related gating are present in the upper limb. As hypothesized, when proprioceptive feedback during a passive movement was relevant to a goal-based response, less gating took place than when the movement was irrelevant, allowing more sensory feedback to ascend to the cortex. Specifically, as measured by the earliest S1-related SEP component (N20-P26), SEPs were the highest in amplitude at rest when no movement was taking place, followed by task-relevant movement, with irrelevant passive movement producing the smallest response in S1. Therefore, not only does the general pattern of movement-related gating affect both the upper and lower limb (1) in a similar manner, but relevancy-based effects can be elicited in both as well. The following discussion will explore the potential neural mechanisms behind both movement-related gating, and the task-relevancy effects associated with it.

6.1.1 Neural Mechanisms Behind Movement-Related Gating

In relation to the current results, the difference in N20-P26 amplitude between rest and a task-irrelevant movement condition may be attributed to peripheral or cortical contributions. The cortical influence on movement-related gating has largely been thought

to arise from M1 (21, 22). Thus, a comparison of both central and peripheral pathways, as well as the activated cortical regions between rest and movement conditions is required.

At rest, when median nerve stimulation is delivered at the wrist, afferent sensory fibres are directly activated, and thus the sensory information ascends through the dorsal-column medial-lemniscal pathway to S1 (39). The first-order neuron enters the dorsal horn of the spinal cord and ascends ipsilaterally in the cuneate tract to the level of the dorsal-column nuclei in the medulla where it synapses in the cuneate nucleus (39). The second-order neuron decussates at the level of the medulla and ascends in the medial-lemniscus to synapse in the VPL of the thalamus (39). Finally, the third-order neuron travels from the VPL to S1 (39). Logically, as sensory information takes the same neuroanatomic path to the cortex regardless of whether an individual is resting or moving, gating of sensory information during movement must be the result of inhibitory influences on or within this pathway.

During passive movement as compared to rest, there are differences in both cortical activation and peripheral receptor activation, which could contribute to the gated levels of sensory feedback that reach the cortex (1). Hoffman-reflexes (H-reflexes), similar to early cortical responses, are attenuated with movement supporting a role for peripheral contributions to movement-related gating (40). Further investigation into these peripheral contributions implicated a presynaptic spinal route resulting from movement-based activation of somatosensory receptors (39). The inhibition of sensory feedback at the level of the spinal cord would translate to smaller cortical responses, as measured by the N20-P26. Therefore, these peripheral receptors would not be activated during a resting

SEP condition in which no movement was taking place, resulting in greater N20-P26 amplitudes being seen when compared to SEPs delivered during movement.

Additionally, cortical contributions largely arising from M1 further this gating effect (21, 22). Neuromagnetic (magnetoencephalography) imaging studies have shown that the cortical areas of activation are largely the same as during active movement, specifically with regards to the sensorimotor cortices (41). As active movement gating patterns have largely been linked to descending control originating in M1, it is logical that gating during passive movement is controlled by similar mechanisms. Therefore, during passive movement M1 may induce gating through PAD at the level of the spinal cord, presynaptic inhibition at the level of the DCN, via the TRN, or through a combination of these, which have been discussed in further detail in the Introduction. During the resting condition in the current experiment, movement was not taking place, thus not activating M1 to exert descending control on these pathways. Both this cortical influence and the aforementioned peripheral influence of movement contribute to the decreased N20-P26 amplitudes seen during the task-irrelevant movement condition, as compared to SEP responses delivered at rest.

6.1.2 Neural Contributions to Task-Relevancy Effects on Movement-Related Gating

In addition to the decrease in amplitude seen between the rest condition and movement conditions, task-relevancy effects were also seen. The task-relevant movement condition, in which individuals attended to the sensory feedback from the passive movement of their left hands and matched this with movement of their right hands, produced higher amplitude N20-P26 components when compared to the task-irrelevant movement condition. The neural mechanisms underlying these relevancy-based

influences on gating are less well documented in the literature than those underlying movement-related gating; however, two potential mechanisms have emerged: selective disinhibition at the level of the spinal cord and facilitation of afferent transmissions at various levels (1). This is in concordance with the section above outlining the peripheral and cortical contributions to gating, as facilitation may occur by altering one, or both of these mechanisms.

Selective disinhibition at the spinal cord may take place through PAD (1). In PAD, the 1a afferent fibre excites a first-order PAD interneuron in the spinal cord (26). This first-order interneuron then excites a second-order inhibitory interneuron, which inhibits the 1a afferent fibre via presynaptic inhibition (26). Tonically, the corticospinal tract, reticulospinal tract, and vestibulospinal tract can influence levels of PAD (Figure 8). Specifically, the reticulospinal tract can, through inhibitory interneurons, inhibit PAD; however, the corticospinal tract has the ability to inhibit the reticulospinal tract, which would lead to a disinhibition of PAD (26). The vestibulospinal tract tonically excites first order PAD interneurons. In addition, the corticospinal tract, through descending control to the spinal cord, can excite interneurons to increase the amount of PAD. Cumulatively, the corticospinal tract has the ability to inhibit or disinhibit PAD and can execute this in a selective manner allowing for some incoming sensory information to be gated out while some information is not (26). Passive movement has been shown to activate M1, which has been implicated in movement-related gating. Therefore, it is possible that this M1 activity also corresponds with corticospinal tract activation to selectively disinhibit relevant sensory information.

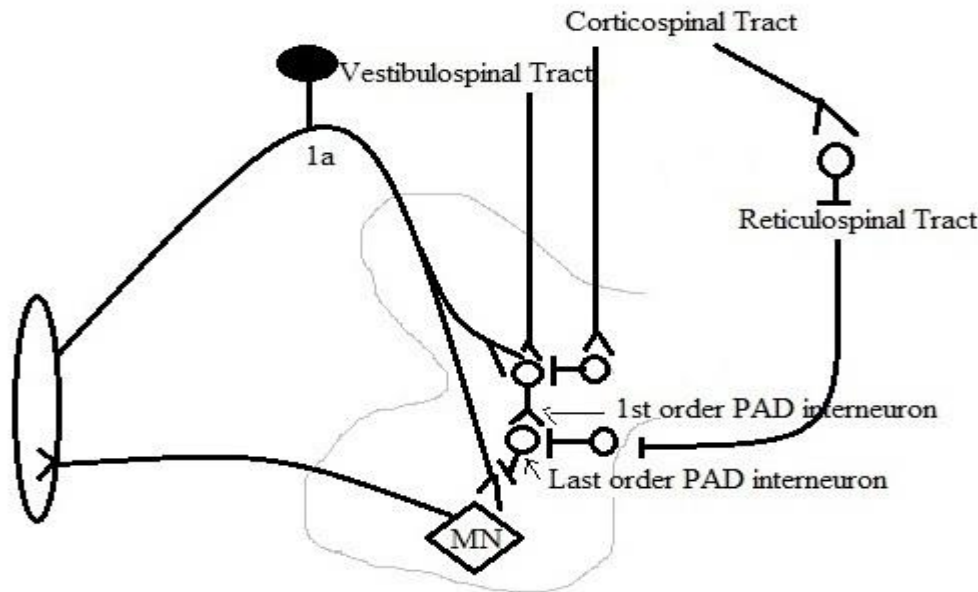


Figure 8: PAD in a cat model. Straight lines indicate inhibition while excitatory synapses are V-shaped. 1st order PAD interneurons receive excitation from 1a afferents and the vestibulospinal tract. 1st order PAD interneurons also receive inhibition from the corticospinal tract. Inhibitory interneurons influencing the 1st order PAD interneuron receive descending tonic inhibition. The reticulospinal tract inhibits the last order PAD interneuron. Three potential mechanisms contributing to tonic levels of PAD are: 1) reticulospinal tract maintaining tonic inhibition on PAD (the corticospinal tract can influence this), 2) disinhibition of PAD interneurons through afferent suppression pathways, 3) tonic vestibulospinal excitation on 1st order PAD interneurons (26).

Of importance when discussing potential mechanisms, H-reflex amplitudes are decreased with passive movement, but task-relevancy does not influence these amplitudes as it does with cortical potentials (42). Therefore, relevancy-based modulation likely occurs following this level of ascension in the dorsal-column medial lemniscal pathway and PAD is not the mechanism by which the task-relevancy effects seen in the current study are being exerted.

Recently, the notion of the TRN, in conjunction with the DLPFC, has emerged as a potential “gatekeeper” controlling the flow of incoming afferent information (43). The TRN links the thalamus with the cortex, and receives information from both locales. The

TRN has been implicated in selective attention tasks due to its location and, through interactions with the thalamus, its ability to regulate both inhibition and disinhibition (44-46). Evidence for the potential role of the TRN in attentional tasks cumulates with the finding that an increase in TRN activity has been shown during pure attentional tasks (47-49). Sensory-based studies have also revealed that the physiological properties of the TRN change during sensory tasks (50-53). As transmission of sensory information passes through the thalamus and is influenced by the TRN, this change in excitability may allow for the modulation at the N20-P26 component.

A recent model suggests that the DLPFC sends excitatory projections to the TRN, which can inhibit the thalamus to prevent distracting information from producing a response (43). More in line with the results of the present study, in which distractors were not present concurrently with relevant information, DLPFC has been modeled as exciting the TRN, which may employ a network of interneurons to increase VPL excitability, thus facilitating sensory information transmitted to S1. As the DLPFC would not be activated during the task-irrelevant movement condition in which attentional demands are negligible, this would explain the discrepancy between S1 excitability (N20-P26 amplitude) in the task-relevant and task-irrelevant conditions. This role of the DLPFC, potentially through TRN connections, on movement-related gating was further explored in the second experiment of this thesis.

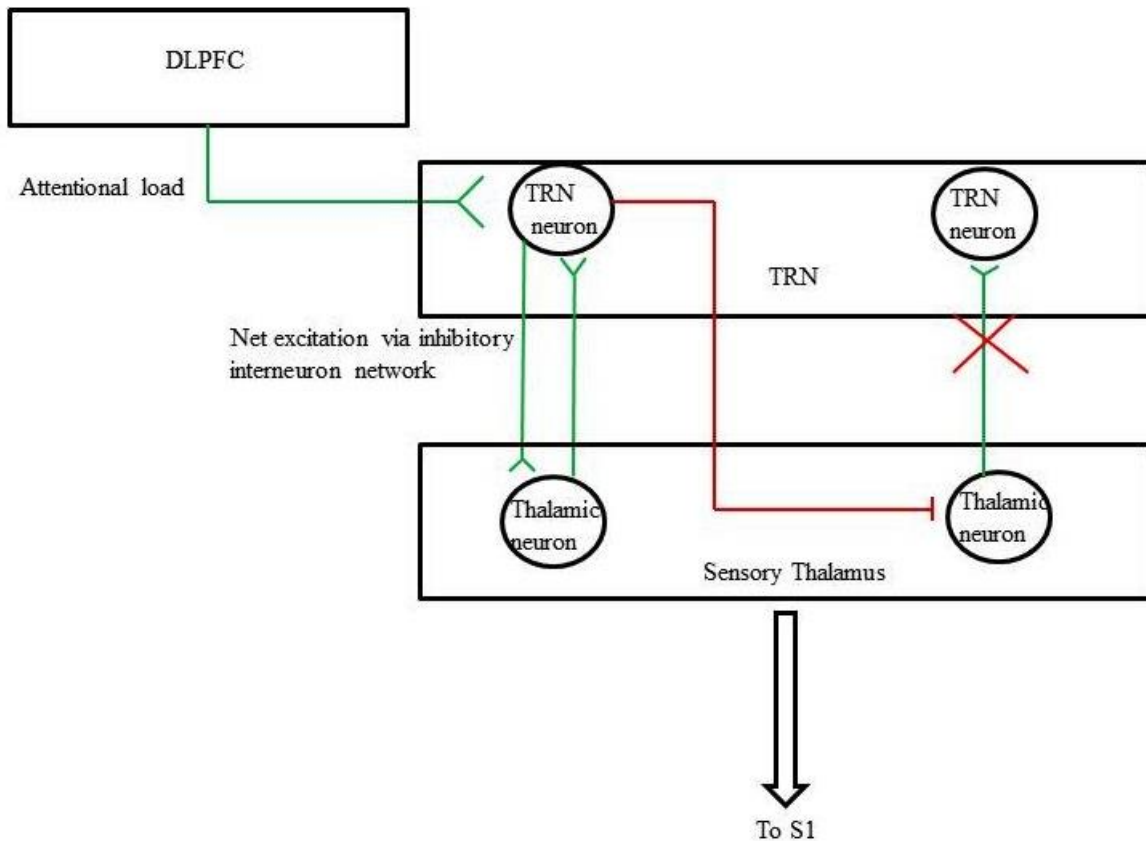


Figure 9: Attentional influences on the TRN and sensory thalamus. Green lines represent excitation. Red lines represent inhibition. Under conditions of high attentional load, the DLPFC and thalamus work together in a rat model. Specifically, the DLPFC shifts attention to relevant events and inhibits neighbouring thalamic-reticular pairs of irrelevant information preventing irrelevant distractions from reaching the cortex, while allowing the transmission of relevant information (54).

6.2 Experiment 2

The second experiment of this thesis employed cTBS to transiently inhibit both the right DLPFC and S1 in order to infer the role of these two cortical areas on task-relevancy influences on movement-related gating. The findings in the current study indicate that both the DLPFC and S1 are integral components required for task-relevancy effects on movement-related gating to occur. If either S1 or DLPFC was functioning, but the other component of the network had been transiently inhibited, task-relevancy modulations on movement-related gating were not seen. In comparison to the data from experiment one, following cTBS over DLPFC or S1, task-relevancy did not augment early component SEP

amplitudes. Movement-related gating; however, remained intact following cTBS over both DLPFC and S1. Resting N20-P26 responses were still greater than those generated during passive movement; however, there was no difference between the task-relevant and task-irrelevant conditions. When comparing the results from the two experiments in this study, the main influence of the stimulation was visible when contrasting the difference between the task-relevant and task-irrelevant movement conditions. The following discussion will examine potential mechanisms underlying the influences exerted by both DLPFC and S1. As cTBS was not administered over M1, the cortical region responsible for movement-related gating effects, the focus of the discussion will be on the task-relevancy based modulations of movement-related gating, rather than the gating itself, as that remained intact following cTBS over both DLPFC and S1.

6.2.1 Neural Mechanisms Underlying Influence of DLPFC on Task-Relevancy Effects on Movement-Related Gating

Following cTBS over the right DLPFC movement-related gating was intact; however, task-relevancy effects on movement-related gating were abolished. The fact that movement-related gating was still present following cTBS over DLPFC suggests that the DLPFC does not exert a tonic inhibition on the somatosensory cortex directly, or via the thalamus. This notion had been hypothesized previously based on the observation that following prefrontal damage, resting SEPs were greater in amplitude than was seen in a control group (6). If tonic inhibition was present, in the current study, a disinhibition of resting SEPs, resulting in greater resting N20-P26 amplitude, would be expected. This was not seen. Therefore, as the DLPFC does not appear to exert a tonic inhibition on the sensory cortex, and SEP amplitude differences are unique to the task-relevancy effects on

movement conditions, our results concur with a proposed selective inhibition or facilitation network underpinning relevancy-based modulation (43).

The most likely proponent to exert the task-relevancy effects on movement-related gating in conjunction with both the DLPFC and S1 is the TRN for a multitude of reasons: the ability to facilitate and inhibit specific information, its known neuroanatomic links with both the DLPFC and S1, and its increased activity levels during both attention and sensory-based tasks (27,45-49). The prefrontal projections to the TRN ensure a cortical component to the gating system, and the TRN then is able to selectively inhibit or disinhibit information based on the attentional feedback from the DLPFC by way of local reticular synapses which allow for inhibition of adjacent subregions within the TRN and thalamus (43). This prefrontal-reticular connection (Figure 10) is also an ideal candidate for influencing transmission of sensory information to the cortex based on the synapses between the two regions; the prefrontal projections terminate in the TRN as both large and small boutons (43). Of particular importance are the large boutons as they contain more synaptic vesicles to be released, making the prefrontal influence more efficient than other areas terminating as small boutons in the TRN (27,28,55-67). Prefrontal-TRN projections are thus neurophysiologically designed to efficiently influence sensory transmission at the thalamic level.

As can be seen in Figure 10, the prefrontal projections to the thalamus overlap substantially with the sensory projections (68). Additionally, the DLPFC projections to the TRN not only synapse in the prefrontal sector of the TRN, but the sensory TRN as well (68). Specifically, when the DLPFC is attending to stimuli, excitatory projections synapse in both areas of the TRN (43). As the TRN is composed of GABAergic cells,

excitation from the cortex or from ascending feedback from the periphery leads to activation of inhibitory TRN neurons, which inhibit an inhibitory thalamic interneuron. The end result is a selective disinhibition of the relevant or salient sensory input, resulting in increased sensory transmission in that specific pathway (43).

The results from this thesis support this prefrontal-reticular model of sensory processing. Transient inhibition resulting from the application of cTBS over DLPFC would disrupt this ability to selectively disinhibit relevant information from reaching the cortex, leading to inhibition of relevant afferents, and thus a decreased response in S1. Specifically, despite S1 still providing excitation to the thalamus and TRN, the prefrontal connections would not activate the TRN to initiate the process of selective disinhibition. The DLPFC following cTBS would no longer be able to initiate the process and communicate with the TRN to modify sensory transmission based on relevancy.

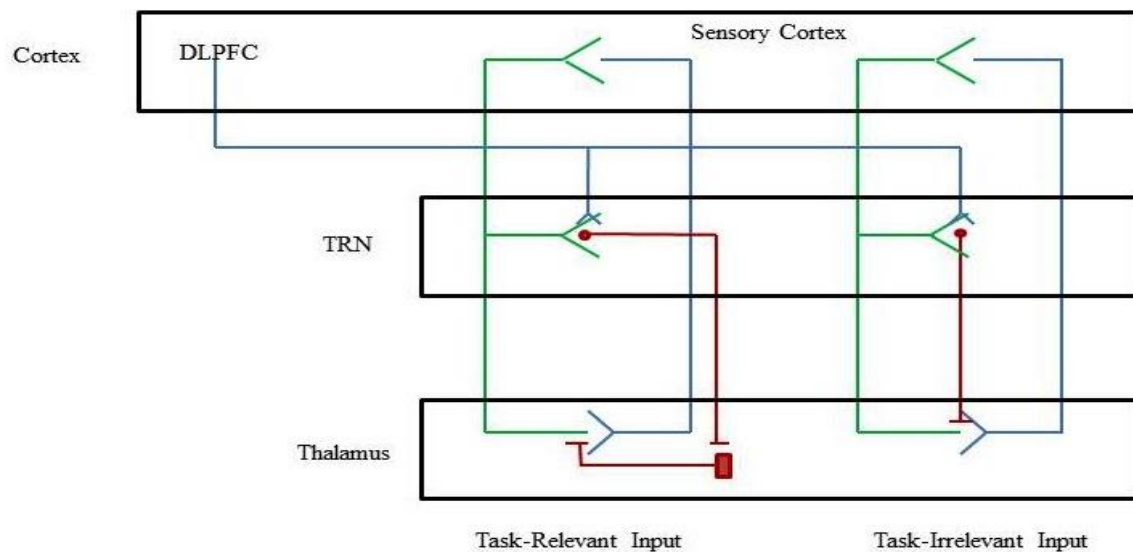


Figure 10: Prefrontal and sensory projections to the TRN and thalamus. Inhibitory synapses are represented by lines. Excitatory synapses are represented by Y-shaped bars. The DLPFC projects to the TRN which then inhibits distracting information from reaching the cortex, by way of a single inhibitory neuron to the pathway between the thalamus and the sensory cortex. The DLPFC and TRN also work together to excite salient or relevant information through a series of inhibitory interneurons. The sensory cortex also has the ability to exert these effects via similar pathways (68).

6.2.2 Neural Mechanisms Underlying Influence of S1 on Task-Relevancy Effects on Movement-Related Gating

The transient inhibition of the sensory cortex by the application cTBS over S1 produced the same results as were seen following stimulation over DLPFC. Resting N20-P26 amplitudes were the highest, with both task-relevant and task-irrelevant movement conditions producing gated responses; task-relevancy based effects were abolished following stimulation. This is in opposition of the hypothesis put forth that following S1 stimulation, the task-relevancy and gating effects would both remain intact. The identical effect of S1 and DLPFC stimulation appear to be indicative of an inter-dependent relationship such that task-relevancy based modulation of sensory information cannot occur when one or the other is not functioning at full capacity.

Neuroanatomically, there is a glutamatergic pathway from S1 layer VI to the thalamus, which is reciprocal in nature (69). These corticothalamic neurons also have branches, which innervate reticular cells (69). As a result, projections from S1 have the ability to directly excite thalamic relay cells, or to indirectly inhibit these relay cells by way of the TRN (69). The projections from S1 to the TRN synapse as small boutons (27,28,55-67). As mentioned previously, the DLPFC terminals are composed of both large and small boutons, with the large boutons being more efficient for intercellular communication (27,28,55-67). When a corticothalamic neuron originating in S1 fires to excite thalamic relay cells, an increase in corticothalamic excitatory post-synaptic potentials (EPSPs) and disynaptic reticular inhibitory post-synaptic potentials (IPSPs) are both seen (69). The opposing influences on selective fibres are a potential mechanism to selectively facilitate or inhibit information arriving in the lemniscal pathway (69). Similarly, a study on the visual system in rats determined that while the visual TRN was

activated with attention, following lesions to the primary visual cortex, this activation was diminished (52). The authors suggest that thalamocortical projections are dependent on corticothalamic pathways to corresponding sensory relay nuclei (52).

In relation to the present study, cTBS applied over S1 to induce transient inhibition would present as temporarily diminished active corticothalamic pathways from S1 to thalamic relay nuclei thus reducing activation in the sensory domain of the TRN. The DLPFC would, with attentional demand, still activate pathways to the TRN, but the impact of these pathways would be reduced due to less excitation from S1. I propose, that the pathways, therefore, work in conjunction with one another to successfully ensure relevant information is able to reach the cortex whereas irrelevant information is filtered out at the level of the TRN.

As is seen in Figure 10, S1 has direct projections to both the TRN and the thalamus itself (VPL). Thus, when S1 is activated, projections to the TRN inhibit distracting input (if present), or inhibit an inhibitory interneuron, which in turn allows transmission of incoming salient input to pass to the cortex (52). In the current study, short-term inhibition of S1, as induced by cTBS, would result in an inability to execute this facilitation of relevant information. While the DLPFC would still be functioning at full capacity and able to thus identify relevant information, it is possible that the DLPFC and S1 must work together to efficiently execute task-relevancy based augmentation of sensory information.

6.3 Limitations

Firstly, a limitation of this study is that cTBS does not allow for a complete blockade of DLPFC activity, but rather temporarily reduces cortical activity. As a result, any findings are not truly indicative of patterns that would be seen if DLPFC or S1 activity was completely absent. An example of this is seen in the DLPFC SEP amplitudes at rest. Following PFC damage, individuals present with higher N20-P26 amplitudes, as compared to controls (6). Given that significant differences emerged across our experimental conditions, this limitation does not significantly detract from the results but it should be considered. For future investigation, individuals who have suffered prefrontal damage, such as stroke, could be examined to understand how individuals with prefrontal neuronal death would respond to a paradigm designed to highlight task-relevancy based modulation of movement-related gating.

Secondly, a potential limitation to this study is that the sample is not representative of the population, which will limit the external validity and generalizability of the study. The convenience sampling approach of recruiting volunteers from the student population at the University of British Columbia attracts individuals in their 20s who are pursuing post-secondary education, or are keenly interested in the research topic. This study is an efficacy study based on understanding a cortical network. Therefore, this sampling technique should not detract from the results. Young participants are essential when examining prefrontal regions, as age may impact this region, regardless of stroke status. Additionally, no extrinsic motivation factors or education level should have any effect on the results as the study measures activation of the somatosensory cortex. Future work should examine age effects on this network.

Thirdly, in attentional studies there is a heavy reliance on participants to follow instructions. There is not a quantitative method by which to measure attentiveness or mind-wandering. Therefore, while our results indicate that some attention was being directed towards relevant stimuli, as is seen in the facilitation of that sensory information, it cannot be definitively stated.

A final limitation of this study is that, in humans, it is not possible to measure TRN activity using EEG. Therefore, while it is postulated that the TRN is highly involved in the path responsible for task-relevancy effects on gating, this cannot be confirmed. More advanced imaging techniques, such as fMRI, may be used to increase our knowledge of the active areas during movement-related gating due to its spatial accuracy.

6.4 Significance

Attentional deficits are a common impairment seen in individuals who suffer strokes. Deficits in somatosensation are also common after stroke and are associated with impaired motor learning (7,70). While this study aims to evaluate the role of the prefrontal cortex in task-relevant movement related gating, it is just an initial step.

Future studies should test the effects of varied attentional conditions on the excitability of the sensory cortex in individuals with prefrontal damage to investigate whether the outcomes transfer to the stroke model. Additionally, examining neural mechanisms following network damage will allow the investigation of the functional relevance of the network. This task-relevancy network needs to be examined in the context of motor learning to determine if regulation of this network can be utilized to compensate for somatosensory deficits after stroke. For example, this prefrontal filter could be regulated to gate out less information, thus heightening somatosensory

information to the cortex. Another clinical application that could be considered is whether motor learning deficits are seen following damage to the prefrontal cortex. Greater understanding of both of these components may enhance our understanding of how brain damage, such as stroke, impacts the integration of sensation into ongoing movement, and may be used to improve rehabilitative techniques.

References

- (1) Staines WR, Brooke JD, McIlroy WE. Task-relevant selective modulation of somatosensory afferent paths from the lower limb. *Neuroreport* 2000 June 5;11(8):1713-1719.
- (2) Bolton DA, Staines WR. Transient inhibition of the dorsolateral prefrontal cortex disrupts attention-based modulation of tactile stimuli at early stages of somatosensory processing. *Neuropsychologia* 2011 Jun;49(7):1928-1937.
- (3) Staines WR, Black SE, Graham SJ, McIlroy WE. Somatosensory gating and recovery from stroke involving the thalamus. *Stroke* 2002 Nov;33(11):2642-2651.
- (4) Cohen LG, Starr A. Localization, timing and specificity of gating of somatosensory evoked potentials during active movement in man. *Brain* 1987;110(Pt 2):451.
- (5) Chapman CE. Active versus passive touch: factors influencing the transmission of somatosensory signals to primary somatosensory cortex. *Can J Physiol Pharmacol* 1994 May;72(5):558-570.
- (6) Yamaguchi S, Knight RT. Gating of somatosensory input by human prefrontal cortex. *Brain Res* 1990 Jun 25;521(1-2):281-288.
- (7) Vidoni ED, Acerra NE, Dao E, Meehan SK, Boyd LA. Role of the primary somatosensory cortex in motor learning: An rTMS study. *Neurobiol Learn Mem* 2010 May 2010;93(4):532-539.
- (8) Huang YZ, Edwards MJ, Rounis E, Bhatia KP, Rothwell JC. Theta burst stimulation of the human motor cortex. *Neuron* 2005 Jan 20;45(2):201-206.
- (9) Giblin DR. Somatosensory evoked potentials in healthy subjects and in patients with lesions of the nervous system. *Annals of the New York Academy of Sciences* 1964;112:93.
- (10) Wasaka T, Nakata H, Kida T, Kakigi R. Changes in the centrifugal gating effect on somatosensory evoked potentials depending on the level of contractile force. *Experimental Brain Research* 2005 September 2005;166(1):118-125.
- (11) Rossi S, Tecchio F, Pasqualetti P, Ulivelli M, Pizzella V, Romani GL, et al. Somatosensory processing during movement observation in humans. *Clinical Neurophysiology* 2002 2002;113(1):16-24.
- (12) Staines WR, Brooke JD, Angerilli PA, McIlroy WE. Generalisability of sensory gating during passive movement of the legs. *Brain Res* 1998;801(1-2) (pp 125-129):ate of Pubaton: 10 Aug 1998.

- (13) Nakata H, Sakamoto K, Yumoto M, Kakigi R. The relationship in gating effects between short-latency and long-latency somatosensory-evoked potentials. *Neuroreport* 2011 21 Dec 2011;22(18):1000-1004.
- (14) Rossini PM, Babiloni C, Babiloni F, Ambrosini A, Onorati P, Carducci F, et al. 'Gating' of human short-latency somatosensory evoked cortical responses during execution of movement. A high resolution electroencephalography study. *Brain Res* 1999;843(1-2) (pp 161-170):ate of Pubaton: 02 Ot 1999.
- (15) Ghez C, Lenzi GL. Modulation of sensory transmission in cat lemniscal system during voluntary movement. *Pflugers Arch* 1971;323(3):273-278.
- (16) Ghez C, Pisa M. Inhibition of afferent transmission in cuneate nucleus during voluntary movement in the cat. *Brain Res* 1972 May 12;40(1):145-155.
- (17) Chapman CE, Jiang W, Lamarre Y. Modulation of lemniscal input during conditioned arm movements in the monkey. *Experimental Brain Research* 1988 1988;72(2):316-334.
- (18) Rushton DN, Rothwell JC, Craggs MD. Gating of somatosensory evoked potentials during different kinds of movement in man. *Brain* 1981 1981;104(3):465-491.
- (19) Abbruzzese G, Ratto S, Favale E, Abbruzzese M. Proprioceptive modulation of somatosensory evoked potentials during active or passive finger movements in man. *Journal of Neurology Neurosurgery and Psychiatry* 1981 1981;44(10):942-949.
- (20) Shin H-, Chapin JK. Modulation of afferent transmission to single neurons in the ventroposterior thalamus during movement in rats. *Neurosci Lett* 1990;108(1-2) (pp 116-120):ate of Pubaton: 1990.
- (21) Jiang W, Lamarre Y, Chapman CE. Modulation of cutaneous cortical evoked potentials during isometric and isotonic contractions in the monkey. *Brain Res* 1990;536(1-2) (pp 69-78):ate of Pubaton: 1990.
- (22) Starr A, Cohen LG. 'Gating' of somatosensory evoked potentials begins before the onset of voluntary movement in man. *Brain Res* 1985 1985;348(1):183-186.
- (23) Canedo A. Primary motor cortex influences on the descending and ascending systems. *Prog Neurobiol* 1997 1997;51(3):287-335.
- (24) Burke RE, Rudomin P, Vyklicky L, Zajac 3, F.E. Primary afferent depolarization and flexion reflexes produced by radiant heat stimulation of the skin. *J Physiol (Lond)* 1971 Feb 1971;213(1):185-214.
- (25) Quevedo J, Eguibar JR, Jimenez I, Rudomin P. Raphe magnus and reticulospinal actions on primary afferent depolarization of group I muscle afferents in the cat. *J Physiol (Lond)* 1995 1995;482(3):623-640.

- (26) Peirrot-Deseilligny E, Burke D. Presynaptic Inhibition of 1a Terminals. The circuitry of the human spinal cord: Its role in motor control and movement disorders; 2005. p. 292.
- (27) Guillery RW, Feig SL, Lozsadi DA. Paying attention to the thalamic reticular nucleus. *Trends Neurosci* 1998 Jan;21(1):28-32.
- (28) Kakei S, Na J, Shinoda Y. Thalamic terminal morphology and distribution of single corticothalamic axons originating from layers 5 and 6 of the cat motor cortex. *J Comp Neurol* 2001;437:170-185.
- (29) Rouiller E, Tanne J, Moret V, Kermadi I, Boussaoud D, Welker E. Dual morphology and topography of corticothalamic terminals originating from the primary, supplementary motor, and dorsal premotor cortical areas in macaque monkeys. *J Comp Neurol* 1998;396:169-185.
- (30) Hurford R, Charidimou A, Foz Z, Cipolotti L, Werring D. Domain-specific trends in cognitive impairment after acute ischemic stroke. *J Neurol* 2013;260(1):237-41.
- (31) Knight RT, Staines WR, Swick D, Chao LL. Prefrontal cortex regulates inhibition and excitation in distributed neural networks. *Acta Psychol (Amst)* 1999 Apr;101(2-3):159-178.
- (32) Skinner, J.E. & Yingling, C.D. Central gating mechanisms that regulate event related potentials and behaviour. *Prog Clin Neurophysiol* 1977;1.
- (33) Du X, Jansen BH. A neural network model of normal and abnormal auditory information processing. *Neural Networks* 2011 August 2011;24(6):568-574.
- (34) Grossheinrich N, Rau A, Pogarell O, Hennig-Fast K, Reinl M, Karch S, et al. Theta burst stimulation of the prefrontal cortex: safety and impact on cognition, mood, and resting electroencephalogram. *Biol Psychiatry* 2009 May 1;65(9):778-784.
- (35) Meehan SK, Lindsell MA, Handy TC, Boyd LA. Interhemispheric enhancement of somatosensory cortical excitability through contralateral repetitive transcranial magnetic stimulation. *Clinical Neurophysiology* 2011 August 2011;122(8):1637-1644.
- (36) Ott DVM, Ullsperger M, Jocham G, Neumann J, Klein TA. Continuous theta-burst stimulation (cTBS) over the lateral prefrontal cortex alters reinforcement learning bias. *Neuroimage* 2011 15 July 2011;57(2):617-623.
- (37) Seniow J, Bilik M, Lesniak M, Waldowski K, Iwanski S, Czlonkowska A. Transcranial magnetic stimulation combined with physiotherapy in rehabilitation of poststroke hemiparesis: A randomized, double-blind, placebo-controlled study. *Neurorehabilitation & Neural Repair* 2012.

- (38) Wassermann EM. Risk and safety of repetitive transcranial magnetic stimulation: Report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5-7, 1996. *Electroencephalography and Clinical Neurophysiology - Evoked Potentials* 1998 January 1998;108(1):1-16.
- (39) Martin J. Descending Motor Pathways and the Motor Function of the Spinal Cord. In: Foltin F, Lebowitz H, Fernando N, editors. *Neuroanatomy: Text and atlas*. 3rd ed. Columbia: McGraw Hill Companies; 2003. p. 230-231.
- (40) Onishi H, Sugawara K, Yamashiro K, Sato D, Suzuki M, Kirimoto H, et al. Neuromagnetic activation following active and passive finger movements. *Brain Behav* 2013;3(2):178-192.
- (41) Cheng J, Brooke J, Misiaszek J, Staines W. The relationship between the kinematics of passive movement, the stretch of extensor muscles of the leg, and change induced gain of soleus H-reflex in humans. *Brain Res* 1995;672(1-2):89-96.
- (42) Brooke J, Cheng J, Collins D, McIlroy W, Misiaszek J, Staines W. Sensori-sensory afferent conditioning with leg movement: gain control in spinal reflex and ascending paths. *Prog Neurobiol* 1997;51(4):393-421.
- (43) Zikopoulos B, Barbas H. Circuits for multisensory integration and attentional modulation through the prefrontal cortex and the thalamic reticular nucleus in primates. *Rev Neurosci* 2007;18(6):417-438.
- (44) Guillery RW, Feig SL, Lozsadi DA. Paying attention to the thalamic reticular nucleus. *Trends Neurosci* 1997 01 Jan 1998;21(1):28-32.
- (45) McAlonan K, Brown D. The thalamic reticular nucleus: more than a sensory nucleus? *Neuroscientist* 2002;8(4):302-305.
- (46) Pinault D. The thalamic reticular nucleus: Structure, function, and concept. *Brain Res* 2004;46(1):1-31.
- (47) Suffczynski P, Kalitzin S, Pfurtscheller G, Lopes da Silva F. Computational model of thalamocortical networks: dynamic control of alpha rhythms in relation to focal attention. *Int J Psychophysiol* 2001;43(1):25-40.
- (48) Vuilleumier P, Hester D, Assal G, Regli F. Unilateral spatial neglect recovery after sequential strokes. *Neurology* 1996;46:184-189.
- (49) Weddell R. Subcortical modulation of spatial attention including evidence that the Sprague effect extends to man. *Brain Cogn* 2004;55:497-506.
- (50) McAlonan K, Cavanaugh J, Wurtz R. Attentional modulation of thalamic reticular neurons. *J Neurosci* 2006;26(16):4444-4450.

- (51) Montero V. Amblyopia decreases activation of the corticogeniculate pathway and visual thalamic reticular nucleus in attentive rats: a focal attention hypothesis. *Neuroscience* 1999;91:805-817.
- (52) Montero V. Attentional activation of the visual thalamic reticular nucleus depends on top-down inputs from primary visual cortex via corticogeniculate pathways. *Brain Res* 2000;864:95-104.
- (53) Montero V. c-fos induction in sensory pathways of rats exploring a novel complex environment: shifts of active thalamic reticular sectors by predominant sensory cues. *Neuroscience* 1997;76:1069-1081.
- (54) Zikopoulos B, Barbas H. Pathways for emotions and attention converge on the thalamic reticular nucleus in primates. *J Neurosci* 2012;32(15):5338-5350.
- (55) Guillery R. Anatomical pathways that link perception and action. *Prog Brain Res* 2005;149:235-56.
- (56) Guillery R. Anatomical evidence concerning the role of the thalamus in corticocortical communication: a brief review. *J Anat* 1995;187:583-592.
- (57) Guillery R, Harting J. Structure and connections of the thalamic reticular nucleus: Advancing views over half a century. *J Comp Neurol* 2003;463:360-371.
- (58) Guillery R, Sherman S. The thalamus as a monitor of motor outputs. *Philosophical Transactions of the Royal Society B: Biological Sciences* 2002;357:1809-1821.
- (59) Rouiller E, Durif C. The dual pattern of corticothalamic projection of the primary auditory cortex in macaque monkey. *Neurosci Lett* 2004;358:49-52.
- (60) Rouiller E, Welker E. Morphology of corticothalamic terminals arising from the auditory cortex of the rat: a Phaseolus vulgaris-leucoagglutinin (PHA-L) tracing study. *Hear Res* 1991;56:179-190.
- (61) Rouiller E, Welker E. A comparative analysis of the morphology of corticothalamic projections in mammals. *Brain Res Bull* 2000;53:727-741.
- (62) Sherman S, Guillery R. The role of the thalamus in the flow of information to the cortex. *Philosophical Transactions of the Royal Society B: Biological Sciences* 2002;357:1695-1708.
- (63) Germuska M, Saha S, Fiala J, Barbas H. Synaptic distinction of laminar specific prefrontal-temporal pathways in primates. *Cereb Cortex* 2006;16:865-875.
- (64) Price J, Lewin G. An ultrastructural size principle. *Neuroscience* ;58:441-446.

- (65) Shepherd G, Harus K. Three dimensional structure and composition of CA3-CA1 axon in rat hippocampal slices: implications for presynaptic connectivity and compartmentalization. *J Neurosci* 1998;18:8300-8310.
- (66) Rosenmund C, Stevens C. Definition of the readily releasable pool of vesicles at hippocampal synapses. *Neuron* 1996;16:1197-1207.
- (67) Murthy V, Synowski T, Stevens C. Heterogeneous release properties of visualized individual hippocampal synapses. *Neuron* ;18:599-612.
- (68) Zikopoulos B, Barbas H. Prefrontal projections to the thalamic reticular nucleus form a unique circuit for attentional mechanisms. *J Neurosci* 2006;26(28):7348-7361.
- (69) Lam Y, Sherman S. Functional organization of the somatosensory cortical layer 6 feedback to the thalamus. *Cereb Cortex* 2010;20(1):13-24.
- (70) Meehan SK, Dao E, Linsdell MA, Boyd LA. Continuous theta burst stimulation over the contralesional sensory and motor cortex enhances motor learning post-stroke. *Neurosci Lett* 2011 Aug 1;500(1):26-30.

Appendix

A. Consent Form

THE UNIVERSITY OF BRITISH COLUMBIA



Title of Study:

The Role of the Prefrontal Cortex in Modulating Task Relevancy Effects of Movement Related Gating Consent Form for Healthy Individuals

Principal Investigator: Lara Boyd, PT, PhD. Department of Physical Therapy, Brain Behaviour Laboratory, Faculty of Medicine, UBC

Co-Investigator: Kate Brown, MSc Candidate, Department of Physical Therapy, Brain Behaviour Laboratory, Faculty of Medicine, UBC

Team Members: Cameron Mang, Katharine Cheung, Katie Wadden, Sonia Brodie, Paul Jones, Michael Borich, Tamara Koren

Invitation to Participate: You are being invited to participate in a research study to determine how sensory training influences motor learning in both stroke patients and healthy controls.

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.

Please take time to read the following information carefully.

Purpose

The purpose of this study is to determine whether brain stimulation that decreases the activity of the dorsolateral prefrontal cortex (DLPFC) will affect which sensory information reaches the brain during movement. These efforts should lead to a better understanding of how specific brain regions work together to highlight the relevant information required to make goal-based movements.

Who Can Participate in this Study?

You have been identified because you are a healthy adult and you are between the ages of 19 and 35 and have the ability to understand English. 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, epilepsy, neurodegenerative disorder, head trauma, or a psychiatric diagnosis. If you are younger than 18 or older than 35 you should not participate in this study. If you are pregnant, claustrophobic (have a fear of enclosed or narrow spaces) or have metallic objects in your body 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 5 visits. The first and second visits will be expected to last 60 minutes. The following three visits will be 90 minutes in duration. There are three main conditions in the final four sessions. The stimulation order on the final three days will be randomly generated according to a random number generator where you will have an equal chance of being placed into any of the three groups. Each day will consist of the same activities but involve different stimulations. One day will involve active stimulation that reduces brain excitability in the DLPFC. One day will involve active stimulation that reduces brain excitability in the primary somatosensory cortex (S1). The final day will involve inactive stimulation as a control condition. During the study you will not know which group you are in on a given day. For the first session, you will be asked to come to the Purdy Pavilion to have an anatomical Magnetic Resonance Image (MRI) which will provide us with a picture of your brain. This is not a diagnostic MRI, but rather will help us in guiding the stimulation you will receive in the laboratory session. For the laboratory session on the second day you will be asked to come to the Brain Behavior Lab (T142a Koerner Pavilion, University of British Columbia) and undergo a brief computer based movement task examining your ability to use feedback from the movement of your upper limbs. This is the same assessment as will be performed immediately after brain stimulation on later days.

For the MRI session you will be asked to come to Purdy Pavilion where one of the research staff will meet you to explain the study. Next, the MRI test will be explained to you before you enter the scanner. You will be asked to leave any metal objects (e.g. watches, bracelets, rings, and metal eyeglasses) at home or in lockers provided in the

waiting room of the MRI centre. You will also be asked to remove any articles of clothing with metal inserts or clasps before entering the magnet room. Please ask the experimenter about anything if you are unsure. You will be positioned on the table of an MRI scanner, lying on your back, and a magnetic resonance (MR) coil (specially designed loop of insulated wire) will be placed near your head. You will then be slid into the centre of the scanner.

It is possible that you may feel uncomfortably confined once inside the MRI machine. This feeling usually passes within a few minutes as the experimenters talk with you and the study begins. However, if this feeling persists, you can tell the investigators over the intercom and you will be removed immediately from the machine. During the scan you will hear banging noises, which are normal. We will ask you to wear headphones or earplugs to ensure that your hearing is not affected by the scan. The scan will take about 15 minutes, with set up time included, the first session should last no more than 30 minutes.

The laboratory aspect of this study involves two variants of Transcranial Magnetic Stimulation (TMS) which will be applied over the outside of your head. TMS affects the brain non-invasively and without pain. In the lab, prior to the application of TMS, we will perform a test that will help to index the effect of brain stimulation. This test will involve the passive movement of your non-dominant limb, as well as a condition in which you will be asked to match this passive movement by actively moving your dominant arm. This test will take about 30 minutes to complete.

The application of TMS will then be used to influence brain excitability. During stimulation you will be seated comfortably in a reclining chair. A figure of eight coil (6 inches long) will be fixed to a frame that will hold it in place over your head. Fifteen minutes of stimulation will be delivered to your brain; this stimulation is painless. However, you may feel a tugging or tingling feeling on your scalp during this time. The application of cTBS immediately following this will last for 40 seconds. After the stimulation bout is completed you will then perform the test that you performed before the TMS stimulation. Again, this test will take about thirty minutes.

Future studies: We would like to know if you are interested in learning about 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

The risks are not greater than the risks in everyday life. These procedures will be conducted according to published safety standards by Dr. Boyd. Dr. Boyd or her associates have discussed this research with you and have described them as follows:

MRI: There is very little known risk associated with undergoing an MRI scan. MRI is used routinely in hospitals around the world. A small number of people may find lying still inside the MR scanner uncomfortable and stressful. If this occurs then you will be brought out of the scanner and the study stopped. Some people are also uncomfortable being in small places (i.e., claustrophobia). Because the MRI scanner is a small space you may also be uncomfortable lying inside it. If you do feel this way you will be brought out of the scanner and the study will be halted. The MRI also makes loud noises that you may find uncomfortable. If you have any metal objects in your body you will not be able to participate in this study. This is because the MRI is a large magnet and can move anything that is metal. The result is that there is the potential for tissue damage associated with dislodging the metal and/or for the objects to become heated during the scan and cause a burn.

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. There is also a small but real risk of seizure in people who do not have epilepsy during TMS brain mapping and treatment. In the event of a seizure you will be referred to a physician who may prescribe medicine and depending upon their diagnosis restrict or suspend driving privileges for a period of time. Safety standards for the application of TMS have been developed and will be followed during this study to minimize the risk. In accordance with these standards the TMS machine will be run at a rate and a frequency that are known to be safe. In addition, Dr Boyd has been trained in the safe application of TMS.

Somatosensory Evoked Potentials (SEP): Collection of SEPs involves application of electrodes to measure muscle activity of the thumb (Electromyography (EMG)) as well as electrodes to measure brain activity applied to the scalp (Electroencephalography (EEG)). All EEG and EMG electrodes are surface electrodes and do not actually contact the skin. A conductive gel provides the contact between the skin and the recording electrodes. In rare instances it is possible that your skin may be sensitive to the conductive gels or rubbing alcohol used for surface recordings. In such cases a skin rash is possible. The very brief electrical stimulation to activate nerves in your wrist can cause a mild tingling sensation. You may stop the procedures for any reason at any time by telling the researcher of any discomfort. This will be effective immediately.

Sensorimotor Task: There are no known risks associated with performing this short-duration computer based task. If at any point you feel uncomfortable you can tell the researchers and they will stop the testing.

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 determining underlying neural networks in the healthy brain. 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.

In the Event of an Injury

In the event you experience a serious side effect during this study during normal business hours, you should immediately contact Dr. Boyd. If it is after 5:00 p.m., a holiday or weekend, you should report to an emergency room. Signing this consent form in no way limits your legal rights against the sponsor, investigators, or anyone else, and you do not release the study doctors or participating institutions from their legal and professional responsibilities. 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.

Withdrawal of Consent

You may withdraw from this study at any time without giving reasons. If you choose to enter the study and then decide to withdraw at a later time, all data collected about you during your enrolment in the study will be retained for analysis.

Confidentiality

Your confidentiality will be respected. However, research records and health or other source records identifying you may be inspected in the presence of the Investigator or his or her designate by representatives of Health Canada and UBC Research Ethics Board for the purpose of monitoring the research. No information or records that disclose your identity will be published without your consent, nor will any information or records that disclose your identity be removed or released without your consent unless required by law.

If the results of this study are published or presented in public, information that identifies you will be removed. If you decide not to sign the form, you cannot be in the study.

Your study-related health information such as which group you have been randomized into will be used at UBC only by Dr. Boyd, and members of her research team who are listed on this consent form. This is important to allow members of the research team to communicate about which group you are participating in for this research. 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 her 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. 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.

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 should either verbally indicate your withdrawal or send a request to Dr. Boyd. The mailing address is Lara Boyd, PT, PhD, University of British Columbia, T-217 – 2277 Wesbrook Mall, Vancouver, BC, V6T 1Z3. If you cancel permission to use your health information, you will be withdrawn from the study. 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

I have been given information about this research study and an explanation of what will be done, how long it will take, and 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.**

My signature on this consent form means:

- I have read and understood the subject information and consent form.
- I have had sufficient time to consider the information provided and to ask for advice if necessary.
- I have had the opportunity to ask questions and have had satisfactory responses to my questions.
- I understand that all of the information collected will be kept confidential and that the results will only be used for scientific objectives.
- I understand that my participation in this study is voluntary and that I am completely free to refuse to participate or to withdraw from this study at any time without changing in any way the quality of care that I receive.
- I authorize access to my health record [if applicable include 'and samples'] as described in this consent form.
- I understand that I am not waiving any of my legal rights as a result of signing this consent form.
- I understand that there is no guarantee that this study will provide any benefits to me

Type/Print Subject's Name

Signature of Subject

Date

Type/Print Name of Witness

Signature of Witness

Date

Type/Print Name of Person Obtaining Consent

Signature of Person Obtaining Consent

Date

Type/Print Name of Principal Investigator

Signature of Principal Investigator

Date

B. Screening Forms

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: _____

Please **CIRCLE ONE**:

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

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

part of the Vancouver Coastal Health Authority

☐ LGH ☐ UBCH ☐ VGH**MAGNETIC RESONANCE IMAGING (MRI)
PATIENT SCREENING FORM**

PCIS LABEL

Every patient scheduled for MRI **MUST** complete the following questionnaire prior to the being scanned. The technologist will be happy to answer any of your questions. **Please answer each question accurately and explain any marked "yes".**

Patient name: _____ Date: _____

Birth date: _____ Age: _____ Weight: _____ kg _____ lbs

Do you have:	Yes	No	Unsure	If yes, explain
Cardiac (Heart) Pacemaker or Wires				
Artificial Heart Valves				
Brain aneurysm clips				
Metal in your eyes (At any time in your life)				
Implanted Electrodes, Pumps or Catheters				
Neurostimulators				
Shrapnel, Bullets or other metal fragments				
Any Tattoos – including permanent make up				
Ear implants (Cochlear, Stapes) /Hearing Aid				
Orthopedic (Bone) Screws, Pins, Plates, Rods				
Breast tissue expander or other implants				
Prosthesis (Eye, Penile, Leg, Arm, Joint, etc.)				
Any Stents, Coils, or Filter in blood vessels				
Dentures, retainer, braces, magnetic implants				
Transdermal medication patches (Examples: Nitroglycerin for heart or Nicotine to stop smoking)				
Body Piercing other than earrings				
Have you ever had surgery or operation on:				
Brain, Eye, or Ear				
Heart				
Neck, Chest, or Back (Spine)				
Abdomen, Pelvis, Hips				
Arms and/or Legs				
Injection into a joint within the last 2 weeks				
Are you:				
Pregnant				
Claustrophobic				

Please remove all your jewelry, watch, credit cards, coins and other metallic items (earrings, hair clips, bobby pins, etc.). A MRI staff member will instruct you about securing your items prior to entry into the examination area. I have read and understand the entire contents of this form. I affirm that the above information is true to the best of my knowledge and I hereby consent to the MRI study

Signature of person completing this form

Date

Relationship to patient if form not completed by patient

Date

Signature of translator

Date

MR Technologist Initials/Date