TASK-SPECIFIC MODULATION OF CORTICOSPINAL EXCITABILITY

TASK-SPECIFIC MODULATION OF CORTICOSPINAL EXCITABILITY DURING ARM AND FINGER MOVEMENTS

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Lay Abstract

On a day to day basis, we perform a variety of movements without giving much thought to how complicated it is for our nervous system to perform said movements. There are many different areas of the brain that are responsible for controlling movement. This dissertation focuses on two key areas that are critical for movement performance, namely the primary motor and somatosensory cortices. The primary motor cortex is largely responsible for sending signals to the muscles to control movement, while the primary somatosensory cortex plays a crucial role in receiving and understanding sensory input from our body. The studies in this dissertation describe how these two areas of the brain communicate during finger and arm movements to produce or prevent muscle activity. This work has implications for individuals with disorders that impact their everyday movements.

Abstract

The main goal of the dissertation was to determine task-dependent modulation of corticospinal descending output. From this main goal, I conducted three different studies to determine how corticospinal output to muscles of the upper arm and hand changed as a function of the task demands. In study 1, I examined how a somatosensory-motor circuit changes when a muscle needs to be active in a task and found that this circuit may be dependent on the movement phase, type of afferent input, and the task demands. In study 2, I examined how this same somatosensory-motor circuit acts to both allow and prevent muscle activity before movement. I revealed that this somatosensory-motor circuit may function to prevent muscle activity when a muscle is not needed in a task and creates facilitation of corticospinal output when it needs to be active in a task. These effects, however, are dependent on the movement phase and the digit the muscle is controlling. Study 3 determined how corticospinal output is modulated to upper arm muscles when performing movements that required different combinations of segmental interactions to achieve the task successfully. Corticospinal output was increased when inertia and the BBC moment at a joint *resisted* the intended joint rotation and these effects were dependent on the muscle and movement phase. I propose a model of the connectivity between the primary motor and somatosensory cortices that would increase, modulate, or decrease corticospinal output to a muscle depending on its role in the task. The findings from this work provides information to guide future neural rehabilitative interventions for individuals who have movement disorders arising from altered somatosensory-motor

processing such as Cerebellar Ataxia, Developmental Coordination Disorder, Focal Hand Dystonia, Parkinson's disease, and stroke.

Keyword: Clinical Neurophysiology, Neural Control of Movement, Transcranial Magnetic Stimulation, Somatosensory-motor integration, Primary Motor Cortex, Primary Somatosensory Cortex, Cortical Circuitry, Task-dependent Cortical Output.

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List of All Abbreviations and Symbols

Ach	=	Acetylcholine
ADM	=	Abductor Digiti Minimi
A-P	=	Anterior to Posterior
APB	=	Abductor Pollicis Brevis
BB	=	Biceps Brachii
BBC	=	Bone on Bone Contact (Moment)
BG	=	Basal Ganglia
Ce	=	Cerebellum
CNS	=	Central Nervous System
d	=	Cohen's d
df	=	Degrees of Freedom
D-waves	=	Direct Waves
EMG	=	Electromyography
EOP	=	EMG Onset Phase
EPSP	=	Excitatory Postsynaptic Potentials
F	=	F statistic
FDI	=	First Dorsal Interosseous
FHD	=	Focal Hand Dystonia
F-max	=	Maximum Force
F-wave	=	Foot wave

GPe	=	Global Pallidus Externus
GPi	=	Global Pallidus Internus
H-reflex	=	Hoffman Reflex
ISI	=	Inter-Stimulus Interval
IPSP	=	Inhibitory Postsynaptic Potentials
I-waves	=	Indirect Waves
LICI	=	Long-Interval Cortical Inhibition
L-M	=	Lateral to Medial
M1	=	Primary Motor Cortex
MEP	=	Motor Evoked Potential
MP	=	Movement Phase
MSO	=	Maximum Stimulator Output
M-wave	=	Direct Motor Response
M-wave max	=	M-wave Maximum
OFC	=	Optimal Feedback Control
p	=	P-Value
P-A	=	Posterior to Anterior
PD	=	Posterior Deltoid
PFC	=	Pre-frontal Cortex
PG	=	Post Go Phase
PM	=	Pectoralis Major
PMP	=	Pre-movement Phase

PNS	=	Peripheral Nerve Stimulation
PPC	=	Posterior Parietal Cortex
PW1	=	Post Warning 1 Phase
PW2	=	Post Warning 2 Phase
r	=	Pearson Product-Moment Correlation Coefficient
rTMS	=	Repetitive Transcranial Magnetic Stimulation
RMT	=	Resting Motor Threshold
S1	=	Primary Somatosensory Cortex
SAI	=	Short-Latency Afferent Inhibition
SD	=	Standard Deviation
SEPs	=	Somatosensory Evoked Potentials
SI	=	Surround Inhibition
SICF	=	Short-Interval Intracortical Facilitation
SICI	=	Short-Interval Intracortical Inhibition
STN	=	Subthalamic Nucleus
t	=	t-statistic
TB	=	Triceps Brachii
TES	=	Transcranial Electrical Stimulation
TMS	=	Transcranial Magnetic Stimulation
TRN	=	Thalamic Reticular Nucleus
$\boldsymbol{\theta_S}$	=	Shoulder angle
$\boldsymbol{\theta_E}$	=	Elbow angle

ω^2	=	Omega Squared
$\bar{X}_{age}$	=	Mean Age
$\bar{X}_{mixed}$	=	Mean Value for the Mixed Nerve
$\bar{X}_{cutaneous}$	=	Mean Value for the Cutaneous Nerve

Declaration of Academic Achievement

Chapter 2 – Published in PLOS ONE

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1.0 Chapter 1: General Introduction and Review of Literature

1.0 General Introduction

The human cortex plays a critical role in voluntary movements. The primary motor cortex (M1) is a large contributor to movement production, but what is often underestimated is the influence of sensory input on motor output. Both animal and human lesion studies point to the fact that sensory input is essential for movement control, particularly when learning new skills or during rehabilitation. Individuals that have disorders with motor symptoms also present with sensory abnormalities. Therefore, to develop effective intervention programs to improve functioning of individuals with certain movement disorders, a basic understanding of circuitry and connections within and between sensory and motor cortical areas is needed. Transcranial magnetic stimulation (TMS) is one method that allows investigators to non-invasively stimulate cortical areas and observe the outcomes in real time. Since the introduction of TMS in 1985, knowledge regarding the functioning of the primary motor cortex has accumulated rapidly, but most research has focused on M1 function while a person is relaxed. Much less is known about how circuitry in M1 is influenced by other cortical areas or in the context of performing movement. Since regaining functional movements in individuals with movement disorders is the end goal of most neural rehabilitative interventions, it is necessary to fully understand how M1 functions during different movements and in the presence of varying sensory inputs.

1.1 Overarching Theme and Goals of the Dissertation

The overarching theme of this dissertation is task-dependent modulation of corticospinal descending output. From this theme, this dissertation addresses three goals. 1.) Is corticospinal descending output modulated prior to and during movement and is this modulation dependent on the movement phase? The answer to this question was determined in studies 1, 2, and 3. 2.) Does the corticospinal descending output depend on muscle involvement in the task? This goal was addressed in studies 2 and 3. 3.) How do cortical circuits contribute to corticospinal descending output modulation during movement and what are the neural mechanisms that mediate these changes? Studies 1, 2, and 3 addressed this question.

1.2 Outline of Experiments

A number of experiments were conducted and organized into three different studies. Study 1 sought to determine how a somatosensory-motor circuit was modulated in the context of performing an isometric finger flexion task with varying sensory inputs and the spinal versus supraspinal origin of these modulations. Study 2 examined how the same somatosensory-motor circuit in Study 1 was modulated in muscles both ‘involved’ as well as ‘uninvolved’ in an isometric finger flexion task. Study 3 determined how corticospinal output to muscles of the upper limb was modulated when performing tasks with varying mechanical interactions between the upper arm and forearm.

1.3 Review of Literature and Method/Instrumentation in Dissertation

1.3.1 Relevant Cortical Physiology and Function

1.3.1.1 Primary Motor Cortex Physiology, Function, and Output

Every day we perform tasks with a high level of skill without having much appreciation for how difficult it is to execute such movements. One important question seeks to understand how our central nervous system (CNS) functions to complete these skilful tasks. To perform a movement, alpha motorneurons must synapse onto extrafusal muscle fibers and cause muscle contraction, ultimately creating the desired movement. The ability of the alpha motorneurons to be depolarized is controlled by output from spinal interneurons, supraspinal structures, and from primary afferents (Canedo, 1997). To understand how movements are controlled, researchers often look towards M1, likely because the majority of corticospinal output neurons arise from M1 (Canedo, 1997) and M1's somatotopy, such that relatively distinct areas of M1 are attributed to one or few body areas.

M1, and the cortex in general, has six cortical layers with each layer containing neurons that play a different functional role. M1 further has a columnar organization that allows communication between the layers that contain different types of neurons (Mountcastle, 1997). Most large corticospinal outputs arise from layer V of M1 and can send both excitatory and inhibitory projections to spinal interneurons contralateral to their origin and allow for the control of movement (Canedo, 1997); there is also a small percentage of output neurons that project directly onto to alpha motorneurons, allowing a strong, non-

interfered signal from the cortex to the muscles (Canedo, 1997). M1 can further influence output to the muscles by sending indirect corticobulbar connections that synapse to subcortical structures, such as the cerebellum, basal ganglia, or thalamus (Canedo, 1997). Although M1 is typically associated with the ability to control descending output to the muscles, it can also control its own input to the cortex. M1's corticospinal output can control gamma motorneuron activity. Gamma motorneurons innervate muscle spindles, which can detect changes in muscle, position, length and velocity and, therefore, M1 can influence the somatosensory input received from the gamma motorneuron system. Further, other corticospinal, corticocortical, or corticobulbar connections can modulate inputs to the cortex at spinal or supraspinal locale (Canedo, 1997). In sum, M1 is a critical area for motor control, as it has the ability to control output to muscles and its own afferent input.

Since M1 plays a crucial role in motor control, researchers have attempted to understand the role of M1 by tying cortical output to motor behaviour. It was hypothesized by Georgopolous and colleagues that M1 codes features of hand motion, such as direction and speed of hand motion (Georgopoulos, Kalaska, Caminiti, & Massey, 1982; Schwartz, 1993). Subsequent research, however, has observed that M1 can code a plethora of movement features, such as joint kinematics, joint torques, joint power, force output, or muscle activity (Scott, Gribble, Graham, & Cabel, 2001; Ajemian, Bullock, & Grossberg, 2000; Herter, Kurtzer, Cabel, Haunts, & Scott, 2007; Scott & Kalaska, 1997; Ashe, 1997; Gribble & Scott, 2002; Morrow & Miller, 2003; Morrow, Jordan, & Miller, 2007).

Further, long trains of M1 stimulation cause non-human primates to perform complex movements, suggesting that M1 may not encode these lower level variables for movement execution, but may coordinate its own circuitry and activity for complex movements (Graziano, Taylor, Moore, & Cooke, 2002; Graziano, Taylor, & Moore, 2002). The compilation of research on M1's functions suggests that this cortical area is essential to effective motor control and it may encode a number of parameters of movement from low level control variables to sophisticated goal-directed actions.

Recently, optimal feedback control (OFC) has been used as a framework for understanding M1 functioning. In the lens of this theory, it could be that M1 may have the ability to encode all the aforementioned movement parameters and M1 may be the locale for complex sensorimotor control (Todorov & Jordan, 2002; Scott, 2004). OFC suggests that movements are performed by defining a task goal and sending the appropriate motor command and motor efference copy to complete the task. Once the movement unfolds, the 'raw' sensory feedback as a result of the movement is compared to the predicted sensory input from the motor efference copy to give an estimation of the 'state' of the body performing the movement. If the state of system indicates that there is a variation in the movement that affects the defined task, a rapid goal-directed correction is made to the motor command. If the variation in the movement does not affect the task goal, however, no rapid correction is made (Todorov & Jordan, 2002; Scott, 2004; Todorov, 2004). OFC is able to describe an abundance of complex behaviours and is suggested to be a helpful tool to understanding the CNS' role in movement control (Scott,

2004). Research has indicated that M1, in particular, does act similar to an optimal feedback controller. Thus, M1 is not only responsible for motor responses, but its function may also be to integrate sensory input (Naito, 2004). Overall, M1 is central to organizing many parameters of movements and, in contrast to previous held beliefs, sensory input is critical to proper M1 functioning.

Evidence from lesion studies also points to the importance of M1 in motor control. In non-human primates, a stroke in M1 causes a disruption in hand function such that fractionated or individualized finger movements are initially impaired (Nudo & Milliken, 1996). Additionally, a stroke to M1 causes a disruption of hand or upper limb movements and the magnitude of the stroke translates to further disruptions in motor control (Schieber, Lang, Reilly, McNulty, & Sirigu, 2009; Fregni & Pascual-Leone, 2006). Although M1 disruption causes abrupt changes in functional movements, the cortex is able to adapt and recover motor control (Jang, 2013). It is likely that undisrupted cortical areas play a critical role in this recovery of function and, therefore, it is important not to forget how other cortical areas also contribute to motor control.

1.3.1.2 Somatosensory Input and the Primary Somatosensory Cortex (S1)

1.3.1.2.1 Functional anatomy and pathway to S1

There are two pathways by which somatosensory input can reach the cortex: the dorsal column-medial meniscus pathway and the spinothalamic tract; this dissertation focuses on inputs from the former pathway. In the dorsal column-medial meniscus pathway,

somatosensory afferents travel through the dorsal horn of the spinal column and project to the medial lemniscus of the medulla of the brainstem in either the cuneate or gracile nuclei –depending on the nature of the afferent input. From this location, the afferents synapse onto neurons which project to the venteral postero-lateral nucleus of the thalamus and synapse onto neurons that project to the primary somatosensory cortex (Mountcastle, 2005). S1 is comprised of Broadmann's areas 1, 2, 3a, and 3b and somatosensory input travels from areas 3 to 2 to 1. Area 3b receives cutaneous input, while 3a receives proprioceptive input (Mountcastle, 2005; Sur, Merzenich, & Kaas, 1980). With the exception of area 3b, all areas of S1 send corticocortical projections to M1 (Jones, Coulter, & Hendry, 1978). Much like M1, S1 also has corticospinal connections that synapse onto interneurons in the spinal column (Lemon, 2008). Therefore, S1 has the ability to control input to M1 even before is traverses more supraspinal structures and may have a role in effective motor control.

1.3.1.2.2 Functional connectivity of S1 to M1

Since S1 has direct projections to M1, it would be expected that neurons within S1 can change the function within M1. It has been shown that S1 projections to M1 can cause a inhibitory post synaptic potentials (ISPS) alone or a rapid excitatory post synaptic potential (ESPS) followed by an ISPS in neurons within the superficial layers of M1 (Ghosh & Porter, 1988). Additionally, tetanic stimulation of S1 neurons can create long term potentiation of neurons within M1 (Iriki, Pavlides, Keller, & Asanuma , 1989), showing that S1 has the capability to create short term and long term changes in M1.

This connectivity has a functional role as well. Cooling of S1 can create difficulty in performing fine motor movements in monkeys (Brinkman, Colebatch, Porter, & York, 1985). In both cats and monkeys, S1 ablation severely impairs the ability to learn new motor skills, but only moderately impairs the performance of already acquired skills (Pavlides, Miyashita, & Asanuma, 1993; Sakamoto, Porter, & Asanuma, 1987). In humans, damage to S1 can impair recovery of motor skills (Abela et al., 2012). Further, plasticity inducing protocols over S1 can mediate changes in M1 (Tsang, Bailey, & Nelson, 2015; Tsang et al., 2014; Jacobs et al., 2014; Jacobs, Premji, & Nelson, 2012; Jacobs et al., 2012; Zapallow et al., 2013). This evidence indicates that S1 can influence M1 activity and is essential for learning new motor skills or refining acquired skills.

1.3.2 Transcranial Magnetic Stimulation (TMS)

1.3.2.1 Introduction to TMS

TMS is a non-invasive method of stimulating the brain and is based on Faraday's law of electromagnetic induction. According to Faraday's law, when a changing magnetic field is exposed to an electrical circuit, an electrical current is induced in circuit. TMS is comprised of a coil of wire and when a high electric current passes through the coil, a magnetic field is produced perpendicular to the direction of the electrical current in the coil. This magnetic field can produce a secondary current, or Eddy current, in a conductive tissue in the opposite direction of the original electrical current (Rothwell et al., 1999; Barker, Jalinous, & Freeston, 1985). When a TMS coil is placed over the scalp, the induced current is produced in the cortex and parallel to the coil (Rothwell et al.,

1999; Hallett, 2007; Barker et al., 1985). TMS stimulators can produce a magnetic field up to 2 Tesla that lasts for 100 μs (Hallett, 2007; Rothwell, Thompson, Day, Boyd, & Marsden, 1991). Typically, the stimulation intensity of a TMS pulse is represented as a percentage of this stimulator maximum (e.g., 2 Tesla).

1.3.2.2 Physiology of TMS

TMS can be used to stimulate any area of the cortex, but for this dissertation, stimulation of M1 was implemented. If the TMS coil is placed over M1 and the stimulation intensity is large enough, it can produce a motor evoked potential (MEP) in targeted muscles. MEPs are typically recorded with surface electromyography (EMG) electrodes and, therefore, the net response of all the neurons, both inhibitory and excitatory, depolarized within the stimulated area is recorded. Typically, the MEP is a measure of a combination of cortical and spinal excitability (Rothwell et al., 1999). The MEP is produced by the summation of ESPS onto the alpha motorneuron due to descending volleys from corticospinal output neurons (Rothwell et al., 1999). Early attempts of brain stimulation used a different method of stimulation known as transcranial electrical stimulation (TES) (Merton & Morton, 1980). TES delivers a current radially to the cortex and is thought to stimulate the corticospinal output neuron directly (Amassian, Quirk, & Stewart, 1990). TES is thought to excite the axon of the corticospinal neuron directly and these inputs to the alpha motor neuron are known direct waves (D-waves) (Amassian et al., 1990; Ziemann & Rothwell, 2000; Patton & Amassian, 1954). These D-waves are recorded as the action potential travels down to the alpha motor neurons. TMS, however, produces

MEPs with longer latencies because the corticospinal output neurons are excited trans-synaptically via inputs from superficial layers of M1, likely layers 2 and 3. These trans-synaptic inputs to the corticospinal output neuron are known as indirect-waves (I-waves) (Patton & Amassian, 1954; Ziemann & Rothwell, 2000). Based on their latency, I-waves are typically numbered with the higher values indicating increasing synapses before projecting onto the corticospinal output neuron (e.g., I1-wave, one synapse; I2-wave, two synapses; I3-wave, three synapses) (Patton & Amassian, 1954). With increasing TMS and TES intensity, both types of stimulation will activate both D and I-waves, but when stimulating at the lowest intensity to elicit a MEP, TMS and TES will preferentially activate I-waves and D-waves, respectively (Di Lazzaro et al., 2004; Di Lazzaro et al., 1998). Because TMS is able to activate excitatory and inhibitory interneurons locally within M1, TMS is sensitive to detecting changes in cortical excitability that TES is not able to do as effectively. For this reason, TMS was used as the primary means of brain stimulation in this dissertation.

1.3.2.3 Orientation, Coil Geometry, Waveform Type of TMS

As discussed in the previous section, TES is thought to preferentially activate D-waves first, while TMS preferentially activates I-waves. Although this is a general description of TES and TMS differences, the orientation of the coil can also influence how the circuitry within M1 can be activated. When the coil is placed over the scalp and the current flows in an anterior to posterior direction, the induced current flows in the cortex in a posterior to anterior direction (P-A orientation). With this orientation, the stimulation

preferentially activates the early I1-waves (Di Lazzaro et al., 1998; Di Lazzaro et al., 2004). If the coil orientation is reversed and the induced current in the cortex flows in the anterior to posterior direction (A-P orientation), the stimulation preferentially activates later I3-waves (Sakai et al., 1997; Di Lazzaro et al., 2001; Ni et al., 2011; Di Lazzaro et al., 2004). One last orientation of the TMS coil that is commonly implemented in the TMS literature and activates the corticospinal output neuron differently is the lateral to medial induced current (L-M orientation). This L-M orientation is thought to preferentially activate the corticospinal output neuron directly similar to, but not exactly like, TES (Di Lazzaro et al., 1998; Werhahn et al., 1994; Di Lazzaro et al., 2004). Of all the TMS orientations, the P-A orientation recruits neurons with the lowest stimulator intensity. Since the P-A orientation stimulates neurons within M1, preferentially activates I1 waves, and requires the lowest stimulator intensity, this orientation was implemented throughout all experiments in the dissertation.

In addition to the orientation of the coil, there are a number of different coil designs that can influence which cortical structures are stimulated. These coil types include a circular coil, cone coil, double cone coil, H-coil, and figure-of-eight coil to name a few. These coils also come in varying size. Of all the designs, the figure-of-eight coil provides the most focal stimulation of the cortex (Rouhonen & Ilmoniemi, 2005). There are also two other waveforms that a TMS pulse can be delivered –biphasic and monophasic waveform pulse. Biphasic pulses delivers a stimulation to the cortex in one direction and also creates a second current in the opposite direction due to self-induction of the coil itself

(Kammer, Beck, Thielscher, Laubis-Herrmann, & Topka, 2001). With the biphasic pulse, it is suspected that a larger population of neurons are stimulated, as evident from changes in measures of cortical excitability between a biphasic and monophasic pulse, but this is dependent on coil orientation and manufacture (Kammer et al., 2001; Brasil-Neto et al., 1992). With a monophasic pulse, the second current that would be produced from self-induction of the coil is slowly dampened. This dampening results in a slower decay of the magnetic field and, therefore, does not stimulate the cortex as much as the second part of the biphasic pulse (Kammer et al., 2001; Barker, Freeston, Jalinous, & Jarratt, 1987). For these above reasons, a monophasic figure-of-eight coil was used in the studies of the dissertation to allow for a more focal cortical stimulation.

1.3.3 Motor Evoked Potentials

M1 has a certain degree of topography such that rather distinct areas have corticospinal projections to muscles controlling different areas of the body. This topography is used to guide where a TMS coil is placed for stimulation of targeted muscles. These areas, however, are not exclusive and there may be overlap between certain body part representations (Fetz & Cheney, 1980; Cheney & Fetz, 1980; Farrell, Burbank, Lettich, & Ojemann, 2007; Schieber & Hibbard, 1993). Therefore, a MEP can be produced in a muscle from multiple stimulation areas within M1 and is an important concept to consider when locating a motor hotspot for TMS stimulation. As mentioned, the MEP that is produced from TMS stimulation is a measure of both cortical and spinal excitability, but there are a number of methods to measure the MEP. Typically, the waveform of the MEP

dictates what measure will be implemented to infer the level of corticospinal excitability. In hand muscles, a common practice in TMS studies is to place one electrode over the muscle belly and one over the metacarpal phalangeal joint (e.g., first dorsal interosseous (FDI), abductor pollicis brevis (APB), and adductor digiti minimi (ADM) muscles). This electrode set-up is similar to a monopolar array and the MEP will be recorded as a biphasic waveform (Winter, 2009). Therefore, it is common to use the peak-to-peak amplitude of the MEP to determine corticospinal excitability. In forearm or upper arm muscles, electrode placement is bipolar with both electrodes over the muscle belly. The resulting MEP from this electrode set-up would be polyphasic (Winter, 2009) and would affect the peak-to-peak amplitude as a measure of corticospinal excitability. A more suitable measure with this electrode array would be to determine the area under the curve of the MEP. It is important to be cognisant of which electrode array and measurement technique is used to record the MEP, as both these factors influence what the researcher can infer about corticospinal excitability.

1.3.4 Motor Threshold

There is inherent variability in the MEP produced from a TMS pulse both within and across participants and it is difficult to standardize the population of neurons being stimulated between participants and over time. One method to control for the population of neurons being stimulated from a single TMS pulse is to normalize the stimulator output to motor threshold (Rossini et al., 1994). In general, motor threshold is defined as the lowest stimulator intensity to elicit a small MEP in the targeted muscle. This threshold

measurement attempts to determine the lowest intensity of the TMS stimulator that sends a descending volley from the cortex down to the spinal cord. There are two different types of motor threshold –active and resting. Active motor threshold involves having a participant maintain a light voluntary contraction (i.e., from 10 to 20% of MVC) and finding the lowest stimulator output that elicits a small MEP (defined by the experimenter; typically between 100 and 200 μV) in the targeted muscle in 5 out of 10 consecutive stimulation trials (Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005; Di Lazzaro et al., 2004). Resting motor threshold (RMT) requires the participant to keep the targeted muscle relaxed and finding the lowest stimulator output that elicits a small MEP (defined by the experimenter; between 50 and 100 μV) in the targeted muscle in 5 out of 10 consecutive stimulation trials (Rothwell et al., 1999; Rossini et al., 1994). There are pros and cons to each motor threshold method. By measuring active motor threshold, there is an increase in spinal excitability and would require a single descending volley to elicit a small motor response; therefore, this method would be more indicative of the 'true' motor threshold (Di Lazzaro et al., 2004; Di Lazzaro et al., 1998). RMT, however, does not require any contraction and therefore, would prevent any fatiguing effects from achieving motor threshold. Because fatigue may influence the cortical circuitry measures obtained in my studies, I chose to use RMT when necessary for my experiments.

1.3.4 Short-Interval Intracortical Inhibition (SICI)

Along with single pulse TMS, there are also other forms of applying cortical stimulation including multiple pulses performed in short succession such as repetitive or paired pulse

TMS. One of these paired pulse stimulation techniques is known as short-interval intracortical inhibition (SICI). SICI occurs when two single TMS pulses are delivered in succession from the same coil and over the same location on the scalp with a short inter-stimulus interval (ISI) or 1 to 6 ms (Kujirai et al., 1993). Specifically, a subthreshold stimulation (i.e., below motor threshold), followed by a suprathreshold stimulation (i.e., above motor threshold), causes a reduction in the MEP amplitude. Evidence from epidural recordings and TES indicate that SICI occurs at the cortical level (Di Lazzaro et al., 1998). SICI does not occur with TES because this type of stimulation excites the corticospinal axon directly and would not be sensitive to cortical changes (i.e., inhibitory interneuron activity changes). Further, epidural recording indicates that the SICI stimulation protocol causes a reduction in the later MEP producing I3 waves (Di Lazzaro et al., 1998). Because the amplitude of the I3 waves are reduced, it is thought that the SICI protocol recruits inhibitory interneurons that produce ISPS onto the excitatory neurons that produce the I3 waves. SICI is thought to act via GABAergic inhibitory interneurons, as ingesting benzodiazepines, which are $GABA_A$ agonists, increases SICI (i.e., more inhibition or larger reduction of the MEP) (Di Lazzaro et al., 2000; Paulus et al., 2008; Ziemann et al., 2014). Overall, SICI measures the state of inhibitory interneurons over the site of stimulation at a given time.

1.3.5 Short-latency Intracortical Facilitation (SICF)

SICF is another form of a paired pulse TMS protocol. Similar to SICI, SICF involves delivering two stimulations from the same TMS coil over the same motor hotspot within

M1. SICF occurs when a two suprathreshold TMS pulses are delivered in succession with a short inter-stimulus interval. The result of this paired pulse stimulation is an increase or facilitation in the MEP size. The timing of the TMS pulses coincides with latency between the descending volleys produces from the single TMS pulse. A typical ISI between simulations is approximately 1.5, 3.0, and 4.5 ms to represent the I1, I2, and I3 waves, respectively (Ziemann et al., 1998; Ilic et al., 2002). This timing would suggest that the SICF protocol increases the I-wave MEP generating circuitry within M1. Pharmacological evidence shows that in the presence of $GABA_A$ agonist, SICF is reduced indicating that fast acting GABAergic inhibitory interneurons can influence this circuit (Ziemann, Tergau, Wischer, Hildebrandt, & Paulus, 1998). In summary, SICF represents the activity of facilitatory networks within M1.

1.3.6 Peripheral Nerve Stimulation

Understanding sensory integration at the cortical level is a complex problem. Providing natural stimulus to sensory receptors causes asynchronous inputs to project to the cortex and, therefore, makes it is difficult for researchers to determine the time course of sensory-motor integration. One method to overcome this problem is to use electrical nerve stimulation to stimulate the nerve directly. This technique typically involves placing a bar electrode over the skin surface under which a nerve lies. The bar electrode is connected to a closed circuit. When stimulation is applied, the nerve is depolarized and an action potential is created in both directions on the nerve. If the action potential travels in the direction the nerve typically transmits information, the action potential is

travelling orthodromic. If the action potential travels in the opposite direction that the nerve typically transmits information, the action potential is travelling antidromic. Additionally, the parameters of stimulation can affect how much information travels along the nerve. Parameters such as the magnitude of current, pulse duration, and frequency of stimulation all impact what the researcher infers based on the results of nerve stimulation (Tsui, 2008). Peripheral nerve stimulation can be used to determine a number of central nervous system functions, but in this dissertation, peripheral nerve stimulation was used for eliciting a direct motor response (M-wave), Hoffman reflexes (H-reflex), and Foot waves (F-waves).

1.3.6.1 M-wave

Applying stimulation to an alpha motorneuron causes both an orthdromic and antidromic response. The orthodromic action potential travels directly to the muscle that the nerve innervates. The M-wave is typically implemented to give information about the maximal motor response that a muscle can obtain. This measure is known as M-wave maximum (M-wave max). In this dissertation, the M-wave maximum measure is used to standardize the intensity of nerve stimulation across time within participants and across participants (Knikou, 2008; Misiaszek, 2003; Hugon, 1973).

1.3.6.2 H-reflex

Applying stimulation over a nerve will stimulate the alpha motorneuron, but will also orthodromically stimulate the afferent nerve (i.e., information travelling toward the

central nervous system). The afferent nerve is comprised of a number of different types including types I, II, III, and IV. An H-reflex occurs when a fast conducting Ia afferent fiber is activated by nerve stimulation and this action potential travels to the dorsal root of the spinal cord and synapses on the alpha motor neurons. With enough EPSP, an action potential will be created on the alpha motorneuron and create a muscular response. The H-reflex is the electrical analog to the stretch reflex, as the Ia afferents represent the muscle spindles that responds to muscle stretching (Hoffmann, 1952). The H-reflex is used as a measure of spinal excitability with high levels in spinal excitability indicating that more outputs to the alpha motorneurons are easily activated (i.e., small amounts of ESPS are required for activation), while a decrease in spinal excitability indicates that outputs to the alpha motorneurons are not easily activated (i.e., large amount of ESPS are required for activation) and could be due to increase inhibition (Knikou, 2008). The state of spinal excitability (i.e., its increased or decreased state) is due to pre and post synaptic from spinal interneurons (Knikou, 2008; Misiaszek, 2003; Zehr, 2002).

When eliciting an H-reflex, it is important to pay attention to the stimulus parameters. As mentioned previously, increasing nerve stimulation intensity will increase size of the M-wave. This stimulation also causes an antidromic action potential to travel up the alpha motor neuron. If an H-reflex is recorded when there is large stimulation intensity, antidromic collision will occur and an H-reflex will not be recorded. Anitdromic collision occurs when the orthodromic action potential on the alpha motorneuron due to the H-reflex collides with the antidromic volley on the alpha motorneuron from nerve

stimulation. For this reason, it is important to be mindful of the stimulation intensity when recording H-reflexes, as it can affect the interpretation of an experiment's results. Typically, the intensity of nerve stimulation to elicit an H-reflex is represented as a percentage of M-wave max and a range of 5 to 30% of M-wave max is used to record an H-reflex.

1.3.6.2 F-wave

An F-wave is another measure of spinal excitability. An F-wave occurs with a supramaximal stimulation (i.e., 125% of the intensity of elicit an M-wave max) of the alpha motorneuron (Mesrati & Vecchierini, 2004; Lin & Floeter, 2004). When the alpha motorneuron is stimulated at such a high intensity, the antidromic volley excites a small proportion of alpha motorneurons and these cells 'back fire' and send an orthodromic response that is recorded in the muscle. In relation to the H-reflex, the F-wave is not as consistent, as each stimulus recruits a different proportion of the alpha motorneuron pool (Mesrati & Vecchierini, 2004; Lin & Floeter, 2004). The benefit of the F-wave is that it can be elicited in hand muscles that are relaxed, while an H-reflex in resting hand muscles is difficulty to obtain. This measure is important because it is able to measure spinal excitability in hand muscles, which are most often used in TMS studies and also can delineate whether changes in a MEP are due to either cortical or spinal excitability changes.

1.3.7 Afferent induced changes in M1 excitability

Stimulating a peripheral nerve is an effective tool for measuring excitability changes at the level of the spinal cord, but this type of stimulation also creates changes in the excitability of M1 circuitry. These circuits can be tested with TMS and each circuit has a temporal relationship with the nerve stimulation. Based on the timing of nerve stimulation and a TMS pulse, alterations in M1 excitability can change from facilitatory to inhibitory. The initial arrival of the nerve stimulation to the cortex causes a short period of inhibition for approximately 10 ms (Tokimura et al., 2000); this circuit is known as short-latency afferent inhibition (SAI). After the initial 10 ms of inhibition, M1's excitability changes to facilitation or remains inhibitory depending on the nerve stimulation intensity and the type of nerve stimulation (Devanne et al., 2009; Fischer & Orth, 2011; Tamburin, Manganotti, Zanette, & Fiaschi, 2001). These medium latency effects last up to 100 ms. After 100 ms, the effects change and create inhibition within M1 and this inhibition can last up to 1000 ms (Chen, Corwell, & Hallett, 1999); this effect is known as long-latency afferent inhibition (LAI). The reproducibility of the medium latency effect and LAI are not consistent across studies (Chen et al., 1999; Classen et al., 2000; Devanne et al., 2009; Tamburin et al., 2001), but the SAI circuit is more robust (Alle, Heidegger, Krivanekova, & Ziemann, 2009; Tokimura et al., 2000; Voller et al., 2006; Udupa, Ni, Gunraj, & Chen, 2013; Richardson et al., 2008; Tsutsumi et al., 2012).

SAI occurs from either a direct projection to M1 from the thalamus or via a relay through S1 (Di Lazzaro & Ziemann, 2013; Tokimura et al., 2000). The SAI circuit is thought to be mediated by cortical mechanisms, as pairing nerve stimulation with TMS at a short ISI causes a reduction in the amplitude of the later I3 waves and TES does not produce as strong levels of inhibition (Tokimura et al., 2000). SAI is thought to be mediated by cholinergic inputs because administration of an acetylcholine (Ach) receptor blockage causes a reduction in SAI (Di Lazzaro et al., 2000). $GABA_A$ agonist lorazepam also reduces SAI (Di Lazzaro, Pilato, Dileone, Tonali, & Ziemann, 2005; Di Lazzaro et al., 2005; Di Lazzaro et al., 2007), suggesting that GABAergic inhibitory interneurons can modify SAI. Since SAI may be a relay through S1, it may be one of the first steps of sensorimotor integration and may function to modify the levels of inhibition and excitation to perform movements effectively.

1.3.8 Surround inhibition

The previous mentioned circuits are measured at 'rest' when a person has complete muscle relaxation (i.e., no muscle activation) and is not performing any tasks. There is one mechanism, however, that is a result of performing a movement; this mechanism is known as 'surround inhibition'. Surround inhibition is a powerful neurophysiological mechanism that focuses neural activity by inhibiting areas surrounding the intended neural response. This mechanism has been observed in the visual (Blakemore, Carpenter, & Georgeson, 1970) and somatosensory (Tamburin, Fiaschi, Andreoli, Marani, & Zanette, 2005) systems, but recent attention has focused on surround inhibition in the

motor system (Sohn & Hallett, 2004; Beck & Hallett, 2011; Beck & Hallett, 2010; Sugawara et al., 2012; Shin, Sohn, & Hallett, 2009; Kassavetis et al., 2012; Voller et al., 2006; Voller et al., 2005). Particularly, surround inhibition in the motor system may be a mechanism that allows for individuated finger movement by enhancing neural activity for muscles performing a task, while inhibiting neural activity for those muscles uninvolved in the task.

Surround inhibition may act through communication with the cortex and basal ganglia. The main components of the basal ganglia are the global pallidus internus (GPi), global pallidus externus (GPe), striatum, substantia nigra, subthalamic nucleus (STN), and nucleus accumbens. The circuits of the basal ganglia may focus intended movements, while preventing unwanted movements through a direct and indirect pathway, respectively. The motor cortex forms a loop with the basal ganglia and the thalamus (Kelly & Strick, 2004). In the direct pathway, motor cortical areas for the intended motor response project to the striatum, the striatum sends an inhibitory projection to the GPi, this striatum to GPi projection disinhibits the GPi to ventral lateral thalamus, which projects to M1; this pathway would allow for further activity in the cortical area for the motor response (Mink, 1996). In the indirect pathway, the striatum sends an inhibitory projection to the GPe and the striatum to GPe projection disinhibits the GPe to STN connection. This disinhibition of the STN allows the excitatory STN projection to the area of GPi responsible for unintended movements to be active, therefore resulting in an inhibition of the thalamus and preventing unintended movements (Mink, 1996). The

substantia nigra compacta and reticulate also play a modulatory role in these pathways via dopamine 1 and 2 receptors and a dysfunction in its activity is thought to be a mechanism underlying Parkinson's Disease (Mink, 1996).

The effect of this loop between the cortex, basal ganglia, and thalamus can be accessed with TMS. If a person is performing a movement such as flexing the index finger, then corticospinal output to muscles surrounding (e.g., abductor pollicis brevis) or in close proximity to the muscles involved in this task (e.g., first dorsal interosseous) should be reduced (i.e., MEPs in the abductor pollicis brevis would be reduced). In fact, this statement is true and is evident in different intrinsic and extrinsic hand muscles (Sohn & Hallett, 2004; Beck & Hallett, 2011). Further understanding of this circuit is important because changes in surround inhibition are applicable to understanding a number of movement disorders such as Parkinson's disease (Shin, Kang, & Sohn, 2007) or Focal Hand Dystonia (Beck et al., 2008; Beck & Hallett, 2011; Richardson et al., 2008).

1.3.9 Modulation of Cortical Circuitry

The aforementioned cortical circuits are typically measured when a person is relaxed with muscles that are silent. SICI, SICF, and SAI circuits can be modified by a number of different methods such as pharmacological interventions, interaction with other cortical networks, or in certain disorders (MacKinnon, Gilley, Weis-McNulty, & Simuni, 2005; Ni, Gunraj, & Chen, 2007; Udupa, Ni, Gunraj, & Chen, 2009; Di Lazzaro et al., 2005; Di Lazzaro et al., 2005; Di Lazzaro et al., 2007; Di Lazzaro et al., 2000; Paulus et al., 2008;

Alle et al., 2009; Udupa et al., 2013; Ni et al., 2011; Chen, 2004; Sailer et al., 2003). The magnitude of surround inhibition is modulated differently during different phases of movement (Sohn & Hallett, 2004; Beck et al., 2008), in the dominant versus non dominant hand (Shin et al., 2009), based on the task complexity (Beck & Hallett, 2010), and force requirement of the movement (Beck, Schubert, Richardson, & Hallett, 2009). Further, surround inhibition can be modulated by practice or experience (Sugawara et al., 2012; Kassavetis et al., 2012). Much less is known about how the SICI, SICF, and SAI cortical circuits act in the context of movement. More information in needed to understand the function of these cortical circuits in the context of performing movements. Further knowledge of the functionality of these circuits during movement can provide the groundwork for future studies evaluating alterations in these circuits in certain movement disorders and guide neural rehabilitation interventions.

1.3.10 M1 Circuitry during movement

To my knowledge, a paucity of research has examined how M1 cortical circuits, tested with TMS, are modulated during movement. No research has examined the changes of SICF in the context of movement. It has been shown that SICI is decreased in a precision grip and this reduction is even greater compared to an isolated contraction (Kouchtir-Devanne, Capaday, Cassim, Derambure, & Devanne, 2012) . SICI has also been shown to be reduced between a ‘warning’ and ‘go’ cue in a reaction time task (Sinclair & Hammond, 2008), but no further alterations are dependent on response expectancy (Sinclair & Hammond, 2009). Further, differences in resting SICI are related to the

performance of a simple reaction time task (Heise et al., 2013). These findings suggest that SICI can be modulated during movement and there may be some task-specific effects of these observed reductions of SICI. There are only a few research studies that have covered how SAI functions during voluntary contraction. During the onset of movement, SAI is reduced when the digit is involved in performing the task (Voller et al., 2006; Richardson et al., 2008). When the digit is in close proximity of a muscle performing the task, however, there are mixed results of SAI's function (Richardson et al., 2008; Voller et al., 2006). During tonic muscle contraction, SAI is reduced when a digit is involved in the task (Ni et al., 2011). It could be that reductions in SAI are associated with allowing a digit to perform a movement, while keeping SAI intact may be to prevent unwanted movement. To support this notion, reduced SAI is correlated with functional recovery from stroke (Di Lazzaro et al., 2012). This dissertation uncovers how M1 circuitry changes as a function of movement and the behaviour consequences of these circuit modulations.

1.4 References

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1.5 Rationale for Study 1

SAI has shown modulations with different pharmaceutical interventions, interacting with different circuits, and after plasticity inducing protocols. There is also research to support the idea that movement can modulate SAI, showing that this cortical circuit has the ability to modify the magnitude of inhibition during voluntary contraction. If true, this evidence would suggest that somatosensory input has the ability to modify M1 output to the muscles at a very short latency (~40 to 48 ms from somatosensory input until EMG changes) and the effects of somatosensory input on M1 may differ during a variety of movements. In support of this statement, using optimal feedback control as a theory of motor control, it has been shown that sensory input, particularly somatosensory input, can create changes in M1 output to the muscles at a very short time frame (~50 to 90 ms) in a task dependent manner. In this first study, I first intended to study if SAI can be modified at different phases of movement. I also studied whether this SAI modulation depended on the nerve being stimulated. Lastly, I sought to determine whether the changes were due to cortical or spinal effects.

2.0 Chapter 2: Short-latency afferent inhibition modulation during finger movement

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2.1 Abstract

When somatosensory input via electrical stimulation of a peripheral nerve precedes a transcranial magnetic stimulation (TMS) pulse over the primary motor cortex (M1) the corticospinal output is substantially reduced, a phenomenon known as short-latency afferent inhibition (SAI). The present study investigated SAI during rest and during pre-movement, phasic and tonic components of movement. Participants were required to perform an index finger flexion reaction time task in response to an auditory cue. In a series of experiments, SAI was evoked from the mixed, median nerve at the wrist or the cutaneous, digital nerve stimulation of the index finger. To assess the spinal versus cortical origin of movement-related modulation of SAI, F-wave amplitudes were measured during rest and the three movement components. Results indicated that SAI was reduced during all movement components compared to rest, an effect that occurred for both nerves stimulated. Pre-movement SAI reduction was primarily attributed to reduced cortical inhibition, while increased spinal excitability additionally contributed to reduced SAI during tonic and phasic components of movement. SAI was differentially modulated across movement components with mixed but not cutaneous nerve stimulation. These findings reveal that SAI is reduced during movement and this reduction begins as early as the preparation to move. Further, these data suggest that the degree of SAI reduction during movement may be specific to the volume and/or composition of afferent input carried by each nerve.

2.2 Introduction

Somatosensory input modulates M1 excitability over a short and long time course. Short term increases or decreases in M1 excitability are evoked following stimulation of the primary somatosensory cortex (S1) in monkeys [1]. Tetanic electrical stimulation of S1 causes long term changes in the excitability of the primary motor cortex (M1) in cats [2]. Somatosensory afference may also influence M1 excitability [3] via direct thalamocortical projections to M1 [4] or via a relay through S1 [5,6]. With the exception of area 3b, S1 has direct connections to M1 [7].

In awake humans, the corticospinal output from M1 to intrinsic hand muscles evoked by a transcranial magnetic stimulation (TMS) pulse is substantially reduced when preceded by peripheral nerve stimulation at a short latency (~20 ms), an effect known as short-latency afferent inhibition (SAI) [8]. The pathway mediating SAI is considered to be of cortical origin, as there is a reduction in the amplitude of later indirect waves (I-wave) [8] that are thought to represent local interneuronal or corticocortical inputs to the corticospinal output neurons in M1 [9]. SAI which occurs with both mixed and cutaneous nerve stimulation [8], is also non-selective for muscles of the hand when the mixed nerve is stimulated [10] but may show somatotopic effects for cutaneous nerve stimulation [11,12]. SAI is dependent on the intensity of the conditioning and test stimuli [10,13] and the size of the receptive field such that when the cutaneous nerve is stimulated for three digits SAI is decreased compared to single digit stimulation [14]. SAI is mediated by cholinergic inputs and is reduced or abolished in the presence of acetylcholine (Ach)

blockers [15]. GABA modulates SAI such that $GABA_A$ agonist lorazepam causes an inhibition of Ach and reduces SAI [16–18]. Which sub-unit is involved in this reduction is still unknown though it is suggested that the alpha-1 subunit might be involved in the decrease of SAI while the alpha-5 subunit of the $GABA_A$ receptor may be implicated in the increase of SAI [16,18,19].

The magnitude of SAI is modifiable. SAI has been shown to interact with a number of other inhibitory circuits such that short-interval intracortical inhibition (SICI), long-interval intracortical inhibition, and short-interval inter-hemispheric inhibition all reduce SAI [20–22]. Movement also modifies the magnitude of SAI. Tonic muscle contraction of the first dorsal interosseous (FDI) muscle substantially reduces SAI from mixed nerve stimulation [13] and phasic contraction of FDI reduces SAI from cutaneous nerve stimulation in some instances [23] but not others [24]. These data suggest that SAI may be sensitive to the phase of the movement. However this suggestion remains inconclusive given that the intensity of the test stimulation in the tonic [13] and phasic [23,24] components were different across these studies. Recently it has been shown that SAI may be a marker for functional recovery from stroke and may provide insight into the mechanism of stroke recovery [25]. As with most studies measuring SAI in patient populations, this study was performed at rest, but it is unknown exactly how SAI is modulated during different movement components. A thorough analysis of SAI during movement in a healthy population is a precursor for studying clinical populations, where SAI may also be abnormally altered during movement.

It is evident that SAI is reduced during movement [13,23] though it is unknown how early in time this modulation begins. In humans there are local changes in M1 inhibitory circuits, such as SICI, as early as the delay period between a 'warning' and 'go' cue [26,27]. In monkeys, the response amplitude of the afferent input is reduced in both the premotor cortex and M1 during the same delay period before the upcoming movement, and increased afferent gating (i.e., reduction in afferent input amplitude) coincides with faster reaction times [28]. In humans, somatosensory evoked potentials (SEPs) are reduced (i.e., gated) during the phasic and tonic components of movement [29] when SAI is also reduced [13,23,24], suggesting that a reduction of afferent input reaching the cortex may also coincide with less SAI (i.e. less inhibition). It remains unclear whether SAI is altered during the delay period between a 'warning' and 'go' cue and if such modulation depends on the submodality of somatosensory input, as median nerve stimulation would carry a larger volume and different content relative to the digital nerve that is predominantly cutaneous [11,30,31].

The purpose of this study was to determine whether SAI is modulated during the pre-movement (between 'warning' and 'go' cue), phasic (onset of muscle activity), and tonic (sustained muscle activity) components of movement, and to determine if such modulation depends on the submodal input used to elicit SAI. To test this, SAI was measured during a simple reaction time task involving phasic and tonic index finger flexion. SAI was evoked from the median nerve and also via index digital nerve

stimulation. To assess the cortical versus spinal origin of the phase-dependency of SAI spinal excitability was measured using F-waves. We hypothesized that SAI would be reduced during all three movement components compared to rest. Specifically, we expected a reduction in SAI prior to movement since afferent input is shown to be reduced during this pre-movement component [28]**.** Further, we hypothesized that compared to the pre-movement component SAI would be further reduced in phasic and tonic components because of increased gating and increases in spinal excitability during these movement phases.

2.3 Methods

2.3.1 Ethics Statement

This study was approved by the Office of Research Ethics at the University of Waterloo and conformed to the *Declaration of Helsinki*. Written informed consent was obtained from all participants in the study.

2.3.2 Participants

Thirty-seven healthy subjects ($\bar{X}_{age}$ = 25.4, SD = 5.0, 25 males) participated. From this subject pool, some individuals participated in more than one study. Two participants took part in all experiments, three participants completed Experiments 1, 3 and 4, one participant completed Experiments 1 and 4, one participant took part in Experiments 1 and 3, and one participant completed both Experiments 1 and 2. For SAI and F-wave

experiments we aimed to collect ten and seven participants, respectively, as used previously [8,23]. All participants were deemed to be right handed as per a modified version of the Edinburgh Handedness Inventory [32].

2.3.3 Electromyography (EMG)

Surface silver-silver chloride EMG electrodes were placed on the skin overlying the first dorsal interosseous (FDI) muscle and the metacarpophalangeal joint of the right hand in a muscle belly-tendon montage. The analog signal from the electrodes was amplified with a gain of 1000, band-pass filtered between 20 and 2500 Hz (Intronix Technologies Corporation Model 2024F, Bolton, Ontario, Canada), and sampled at a frequency of 5000 Hz using an analog-to-digital interface (Power 1401, Cambridge Electronic Design, Cambridge, UK). The EMG electrodes were used to measure the peak-to-peak amplitude of the motor evoked potential (MEP) recorded from FDI of the right hand. Analysis was completed off-line on a personal computer using Signal software (Cambridge Electronic Design, Cambridge, UK).

2.3.4 Peripheral Nerve Stimulation (PNS)

Peripheral nerve stimulation was achieved with 200 μs square wave pulses delivered via a Grass SD9 Telefactor stimulator (Grass Technologies, West Warwick, USA). The right ulnar or median nerve was stimulated at the wrist with the cathode proximal to the anode and the anode positioned ~ 8 cm proximal to the thenar muscles. The ulnar nerve was stimulated at 25% higher than the minimum stimulator intensity required to evoke a

maximal motor response in FDI muscle and was used to evoke F-waves [33]. The median nerve was stimulated at motor threshold defined as the lowest stimulator intensity to produce a slight twitch in the thenar muscles of the right hand, an intensity used to evoke SAI in past work [8]. The digital nerve of the index finger was stimulated using ring electrodes with the cathode proximal to the anode and positioned around the proximal and intermediate phalynx. The digital nerve was stimulated at ~ 2 times perceptual threshold, an intensity shown to evoke SAI at rest [8].

2.3.5 Transcranial Magnetic Stimulation (TMS)

TMS was delivered using a custom built 50 mm diameter figure-of-eight branding coil connected to a Magstim 200^2 stimulator (Magstim, Whitland, UK). The position and orientation of the coil was monitored throughout the experiment using Brainsight Neuronavigation (Rogue Research, Montreal, Canada) with optical sensors placed on the coil and the participant. The TMS coil delivered a monophasic pulse over the optimal location to elicit MEPs in the relaxed right FDI at 45° in relation to the parasagittal plane to induce a posterior-lateral to anterior-medial current in the cortex and preferentially activate corticospinal neurons trans-synaptically [34]. The resting motor threshold (RMT) was defined as the lowest stimulator intensity to produce MEPs in the FDI of at least 50 μV in 5 out of 10 consecutive trials [35].

2.3.6 Task Preparation

An identical behavioural task was performed in all experiments. Participants performed a simple reaction time task with the response being an isometric index finger flexion to 10% of their maximum force (F_{max}). To determine 10% F_{max} participants were seated with their right arm relaxed with their shoulder abducted ~ 20° and elbow flexed at ~ 90°. In this position, participants voluntarily flexed their index finger at the metacarpophalangeal joint maximally against a load cell (Transducer Techniques, model THA-50-Q load cell). Once the maximal force was identified, participants practiced producing 10% of their maximal index finger force (10% F_{max}) using visual feedback of their force displayed on an oscilloscope. Participants were given at least 5 practice trials in which the experimenter inspected whether they could reach 10% F_{max} quickly and without substantially over- or under-shooting the desired force level. If the participant needed more trials to obtain this level of success, more training trials were given. For the simple reaction time task, each trial consisted of an auditory tone that served as the 'warning' cue followed 3 to 5 seconds later by a second auditory tone that served as the 'go' cue (*Figure 2.1*). Upon hearing the 'go' cue, participants flexed the index finger to 10% F_{max} with the emphasis on speed and held this contraction until instructed by the experimenter to release their force and return to the initial resting state. The voltage from the load cell was passed through a strain amplifier and the force level was displayed on an oscilloscope as a bright line. Subjects were required to position one line, representing their current force level, over a second line that marked their 10% F_{max}.

2.3.7 Experiment 1: Median nerve SAI

Fourteen subjects participated. SAI was investigated in four conditions: rest, pre-movement, phasic and tonic. During the rest trials, participants were required to relax their hand completely. The experimenter monitored the EMG level rejecting any trials in which there was EMG peak-to-peak amplitude > 20 μV before the TMS pulse. In the pre-movement trials, a single TMS pulse was delivered one second before the go cue (*Figure 2.1*) and trials were rejected when there was EMG peak-to-peak amplitude > 20 μV two seconds before the TMS pulse. For phasic trials, the TMS pulse was delivered after the 'go' cue and was computer-controlled using a sequencer file in Signal software such that the TMS pulse would automatically be triggered when the EMG from FDI reached a 100 μV threshold. In the tonic trials, the TMS pulse was delivered once the participant consistently held the 10% F_{max} as determined visually by the experimenter monitoring the force level on the oscilloscope. The TMS pulse in the tonic condition occurred approximately 2 seconds after the participant maintained the targeted force, but was moderately varied across subjects due to differences in the time needed to obtain the required level of force across participants. In addition, we included 'no stimulation' trials within each block that omitted median nerve and cortex stimulation and were intended to remove any anticipatory effects of brain or nerve stimulation during performance of the trials**.** The movement trials and no stimulation trials were presented randomly in two blocks of 40 trials that were separated by a 2 minute break. The inter-trial interval was randomized to occur between 7 and 9 seconds. The rest trials, also repeated twenty times, were completed either before or after the two blocks of 40 trials, an order that was

counterbalanced across participants. The rest trials were isolated from the movement trials to ensure that testing was performed in the absence of the task to eliminate any movement preparation effects, similar to that performed elsewhere [23,36]. Within the twenty trials for each movement component (i.e., rest, pre-movement, phasic and tonic), ten trials delivered TMS pulses only (i.e. unconditioned MEP) and the other ten delivered stimulation to the median nerve 22 ms prior to the TMS pulse to evoke SAI (i.e. conditioned MEP) [13]. Conditioned and unconditioned trials were presented randomly. The stimulator output was adjusted to elicit a MEP of ~1 mV in each individual movement component: rest, pre-movement, phasic and tonic. To achieve this, the stimulator output required to evoke an average of ~ 1 mV MEP across ten trials for each movement component was determined during the experimental set-up and this intensity was kept constant throughout the testing trials. There was no adjustment of the TMS stimulator output on a trial-to-trial basis because the running average of MEPs during the movement components could not be determined online. Prior to beginning the testing trials, practice trials for each movement condition were performed to allow participants to familiarize themselves with the TMS and nerve stimuli in the context of performing the task.

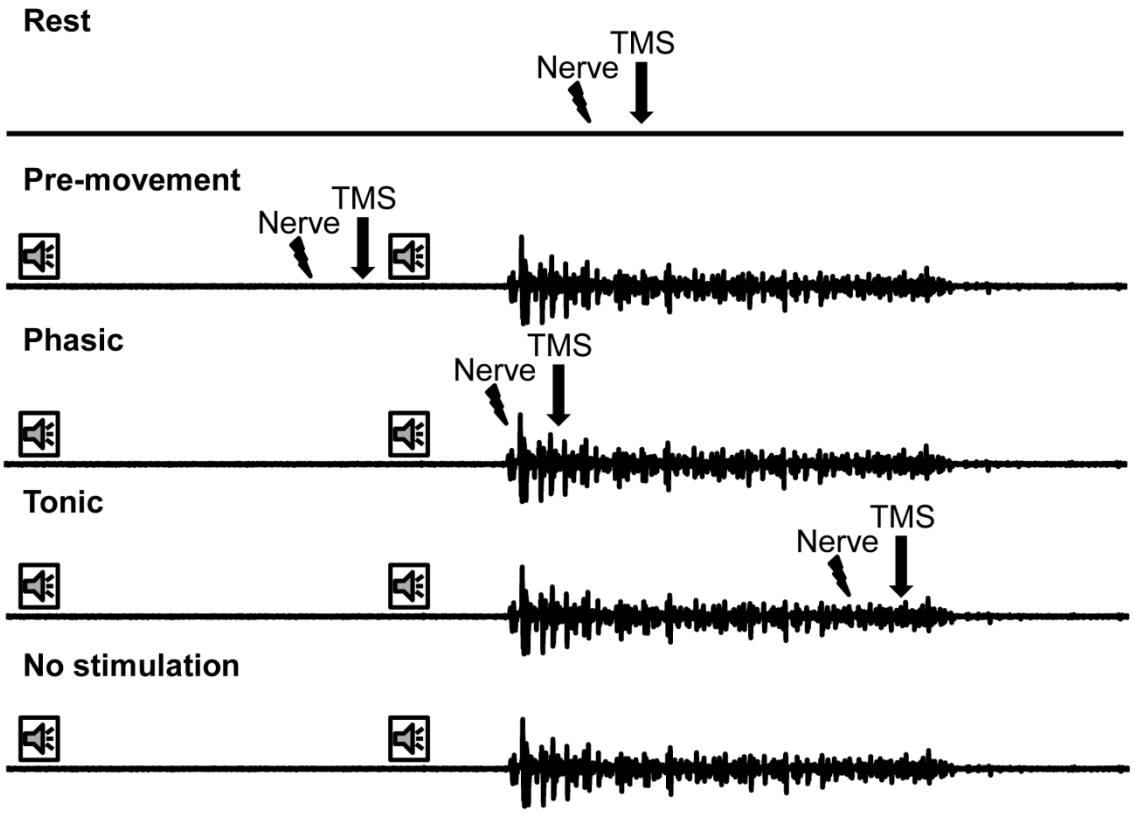

Figure 2.1. Task conditions. The timeline of the rest, pre-movement, phasic, tonic, and no stimulation conditions. The first and second speaker icons represent the 'warning' and 'go' cue, respectively. The timing of the nerve stimulation and TMS pulse are shown schematically.

2.3.8 Experiment 2: Digital nerve SAI

Fifteen subjects participated in Experiment 2. Experiment 2 was identical to Experiment 1 with the exception that the digital nerve of the right index finger was stimulated. The TMS pulse was delivered 25 ms following digital nerve stimulation to elicit SAI [37].

2.3.9 Experiment 3: Spinal excitability during different components of movement

Seven subjects participated in Experiment 3. F-waves were evoked in FDI by stimulating the ulnar nerve at the wrist. A total of 320 ulnar nerve stimuli were delivered throughout the course of this experiment –80 stimuli for each movement component outlined in Experiment 1 (i.e., rest, pre-movement, phasic, tonic). The average of the first twenty F-waves ≥ 20 μV were used for the analysis as performed elsewhere [38]. We delivered 80 stimuli because the persistence of F-wave appearance is approximately 70% for the ulnar nerve [33] and since an F-wave may not appear on every trial, at least 60 electrical stimulations are needed to obtain at least 20 F-waves for averaging [33]. F-waves are a suitable measure for assessing spinal excitability in intrinsic hand muscles [33], where an H-reflex is difficult to produce. The F-waves were elicited at the identical time points as shown by the word 'TMS' in *Figure 2.1*. Similar to Experiments 1 and 2 the rest trials were presented before or after the movement trials and counterbalanced across subjects.

2.3.10 Experiment 4: Mixed nerve SAI with TMS at 1.2 RMT

Twelve subjects participated. Experiment 4 was identical to Experiment 1 with the exception of the TMS intensity. The intensity of the TMS pulse was set to 1.2 RMT in all movement components (i.e., rest, pre-movement, phasic, tonic). Past research has demonstrated 1.2 RMT versus ~ 1 mV normalization yielded similar results when comparing rest to tonic contraction [13]. Experiment 4 investigated whether the 1.2 RMT methodology yielded similar results as Experiment 1.

2.4 Statistical analysis

SAI was expressed as a ratio of the peak-to-peak amplitude of the conditioned MEP (TMS pulse plus nerve stimulation) to the peak-to-peak amplitude of the unconditioned MEP (TMS pulse only). If SAI did not exist at rest (i.e., the ratio of the conditioned to unconditioned MEP was ≥ 1) the participant's data were not included in subsequent analyses. Spinal excitability was determined by the peak-to-peak amplitude of the F-wave.

All experiments used a repeated measures ANOVA with factor PHASE (rest, pre-movement, phasic, tonic). The hypotheses of reduced SAI during the components of movement were tested using *a priori* dependent samples *t*-tests to determine differences between individual components of the movement (i.e., rest versus pre-movement, tonic and phasic; pre-movement versus phasic and tonic). If a significant main effect of PHASE was found for spinal excitability, Tukey's post hoc analysis was performed. Sphericity was tested for all of the repeated measures ANOVA and when this assumption was violated the Greenhouse Geisser correction was implemented. For all statistical tests, the alpha level was set at $p \leq 0.05$.

Aside from the main analyses, a number of additional analyses were performed. First, changes in unconditioned MEP amplitude may lead to changes in SAI [13]. For this reason, to determine if there was a difference in the average peak-to-peak amplitude of the unconditioned MEPs across the different movement components, a repeated measures

ANOVA with the factor PHASE, followed by a post hoc Tukey's test was performed on the unconditioned MEP amplitudes. Second, to determine if SAI existed in each phase, dependent samples *t*-tests were used for each component of the movement (i.e., pre-movement, phasic, tonic) by comparing the means of the conditioned and unconditioned MEP. Third, to determine if there were differences in the degree of SAI between digital versus mixed nerve stimulation in each condition (i.e., rest, pre-movement, phasic, tonic) independent samples *t*-tests were administered. Since three participants completed Experiments 1 and 2, two of the participants were removed from Experiment 1, while the other was removed from Experiment 2 for this analysis only. Last, changes in SAI during the pre-movement component may correlate with reaction time, as gating of afferent input prior to movement coincides with faster reaction times [28]. Therefore, we examined whether reaction time correlated with the degree of SAI in the pre-movement component. Reaction time was defined as the time elapsed between the onset of the 'Go' cue and the EMG 100 μV threshold for trials in which SAI was tested during the pre-movement component.

2.5 Results

2.5.1 Experiment 1: Median nerve SAI

Experiment 1 tested whether SAI was altered during the different components of movement using median nerve stimulation. Three participants were excluded from the study because they did not exhibit SAI at rest. The remaining eleven subjects were

included in the analysis ($\bar{X}_{age}$ = 25.4, SD = 5.5, 8 males). The group average of percentage of maximal stimulator output (MSO) for the rest, pre-movement, phasic, and tonic components was 54.8%, 54.4%, 35.5%, and 42.2%, respectively. Mean 10% F_{max} across these participants was 3.58 N $\pm$ 0.58. *Figure 2.2* displays the group-averaged data (with standard error of the mean) for each movement component. Repeated measures ANOVA revealed a significant main effect of PHASE ($F_{(3,30)}$ = 7.420, p = 0.009). *A priori* comparisons revealed that SAI was reduced in all components of movement compared to rest (pre-movement p = 0.007, phasic p = 0.001, tonic p = 0.002), and comparing among the movement components, SAI was reduced in phasic versus pre-movement condition (p = 0.021). Paired *t*-tests revealed that SAI existed during pre-movement (p < 0.0001), and tonic (p = 0.026), but not during the phasic component of movement (p = 0.10). Last, the peak-to-peak amplitude of the unconditioned MEPs were not different across the conditions ($F_{(3,30)}$ = 0.826, p = 0.49) meaning that the test stimulation amplitude was successfully normalized across the conditions. To ensure that the magnitude of the unconditioned MEP amplitudes did not affect the degree of SAI, a Pearson's correlation coefficient was performed on the averaged unconditioned MEP amplitude and degree of SAI for each participant and revealed no significant correlation (r = -0.049, p = 0.754). These analyses are important since a larger unconditioned MEP could lead to reduced SAI [13] and these data indicate that changes in SAI are related to the movement component rather than the amplitude of the unconditioned MEP. Last, the average reaction time across individuals was 263 $\pm$ 19 ms and did not significantly correlate with the degree of SAI in the pre-movement component (r = -0.001, p = 0.99).

In summary, there was reduced SAI during all movement components compared to rest and in the phasic compared pre-movement component without any changes in unconditioned MEP amplitudes in each respective component.

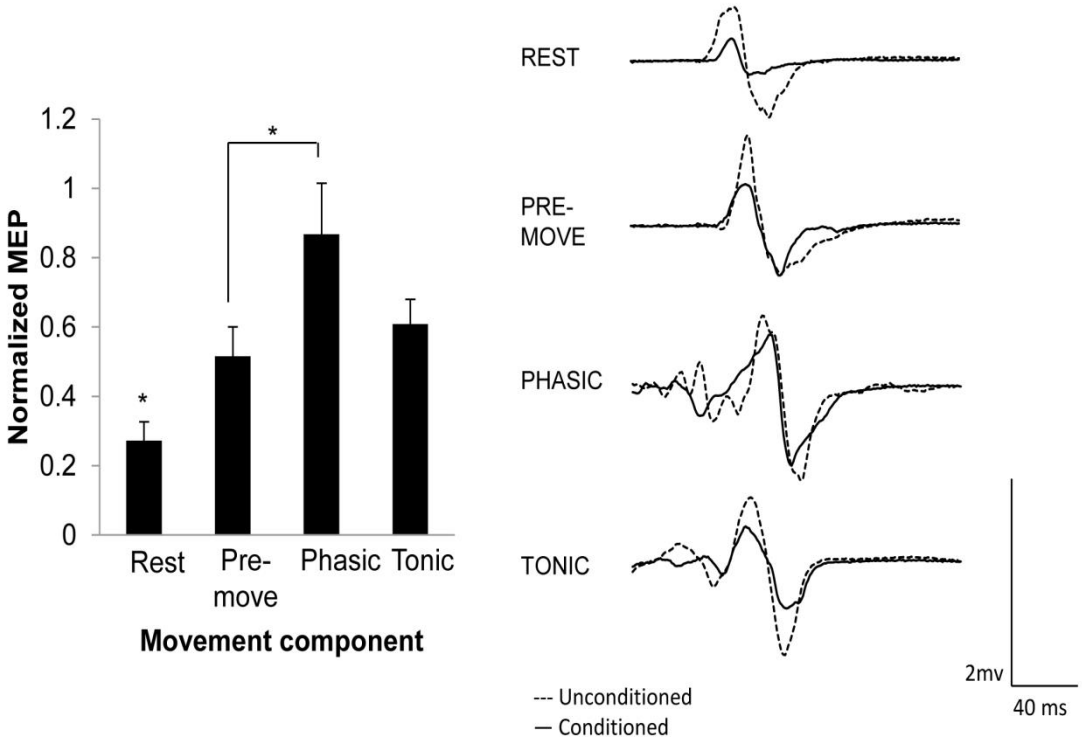

Figure 2.2. SAI induced by mixed nerve stimulation during different components of movement with TMS normalized to ~ 1 mV. Left: Group-averaged data (with standard error of the mean) for rest and each component of movement. Right: individual trial EMG traces from one participant demonstrating changes in SAI across task conditions. An asterisk over a single component of movement indicates it was significantly different than all other components of the movement. An asterisk over a bar connecting two components of movement indicates those phases are significantly different. Significant differences were tested at $p \leq 0.05$.

2.5.2 Experiment 2: Digital nerve SAI

Experiment 2 tested whether SAI evoked by digital nerve stimulation was altered during the different components of movement. Four subjects did not show SAI at rest and the data from the remaining eleven subjects were used in the analysis ($\bar{X}_{age}$ = 22.4, SD = 3.1, 4 females). The group average percentage of maximal stimulator output (MSO) for the rest, pre-movement, phasic, and tonic components were 57%, 56.3%, 35.1%, and 41.3%, respectively. Mean 10% F_{max} across these participants was 3.82 N $\pm$ 0.39. *Figure 2.3* displays the group-averaged means (with standard error of the mean) for each component of the movement. Repeated measures ANOVA revealed a significant main effect of PHASE ($F_{(3,30)}$ = 4.047, p = 0.016). *A priori* comparisons revealed that, similar to the mixed nerve, SAI was reduced in all components of movement compared to rest (pre-movement p = 0.04, phasic p = 0.02, tonic p = 0.004). There was, however, no difference in the magnitude of SAI between the different components of movement. In addition, the paired comparisons revealed that SAI existed during pre-movement (p = 0.03), but not the phasic (p = 0.14) or tonic (p = 0.18) components of movement. Last, the repeated measures ANOVA for unconditioned MEP peak-to-peak amplitude did not reveal a significant main effect for PHASE ($F_{(3,30)}$ = 3.672, p = 0.06). To ensure that the magnitude of the unconditioned MEP amplitudes did not affect the degree of SAI, a Pearson's correlation coefficient was performed on the averaged unconditioned MEP amplitude and degree of SAI for each participant and revealed no significant correlation (r = -0.11, p = 0.478) indicating that the magnitude of the unconditioned MEPs in this range did not relate to the degree of SAI and the differences in SAI depend on the

component of the movement. Last, the average reaction time across all participants was 234 ± 19 ms and did not correlate with the degree of SAI in the pre-movement component ($r = 0.27$, $p = 0.43$). In summary SAI was reduced during all components of movement compared to rest without changes in unconditioned MEP amplitude.

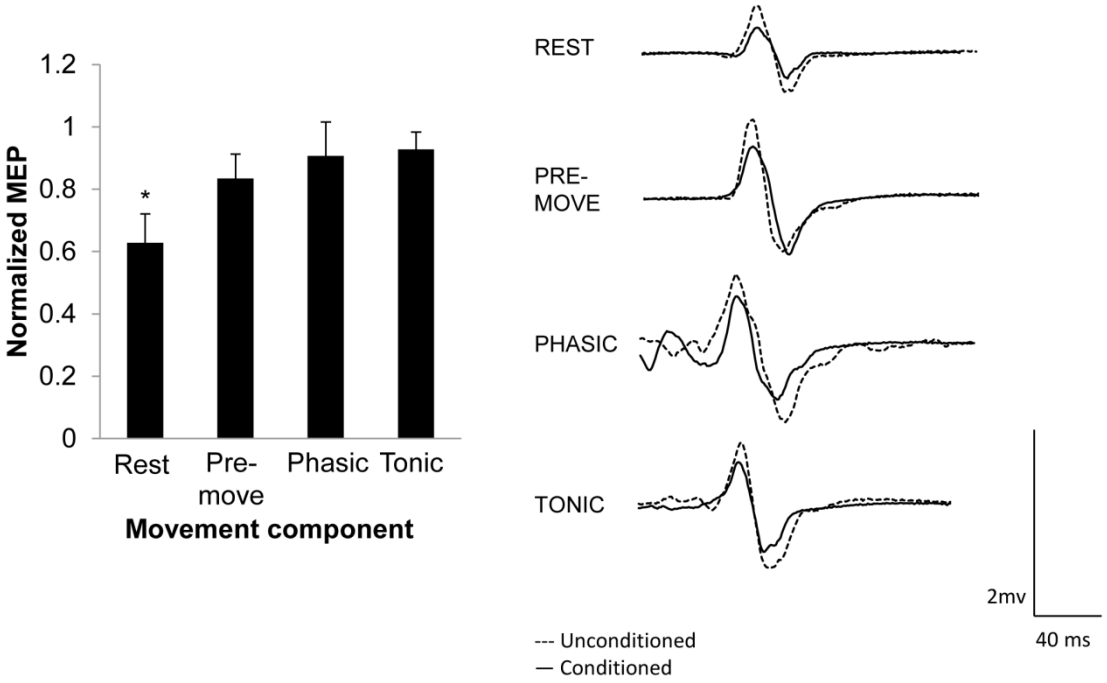

Figure 2.3. SAI induced by cutaneous nerve stimulation during different components of movement with TMS normalized to ~1 mV. Left: Group-averaged data (with standard error of the mean) for rest and each component of movement. Right: individual trial EMG traces from one participant demonstrating changes in SAI across task conditions. An asterisk over a single component of movement indicates it was significantly different than all other components of the movement. Significant differences were tested at $p \leq 0.05$.

2.5.3 Comparison of SAI in Experiments 1 and 2

To determine if there were differences in the degree of SAI between the mixed versus cutaneous nerve stimulated in Experiment 1 and 2, respectively, independent samples *t*-tests were performed. Differences in SAI between the nerves existed such that there was less SAI, meaning less inhibition, when the cutaneous nerve was stimulated versus the mixed nerve in the rest ($\bar{X}_{\text{mixed}} = 0.32$ vs. $\bar{X}_{\text{cutaneous}} = 0.60$, $p = 0.01$), pre-movement ($\bar{X}_{\text{mixed}} = 0.55$ vs. $\bar{X}_{\text{cutaneous}} = 0.80$, $p = 0.04$), and tonic ($\bar{X}_{\text{mixed}} = 0.58$ vs. $\bar{X}_{\text{cutaneous}} = 0.95$, $p = 0.001$) conditions, but there were no differences between the nerves for the phasic condition ($\bar{X}_{\text{mixed}} = 0.90$ vs. $\bar{X}_{\text{cutaneous}} = 0.96$, $p = 0.743$).

2.5.4 Experiment 3: Spinal excitability during different components of movement

Seven subjects completed Experiment 3 ($\bar{X}_{\text{age}} = 25.86$, SD = 2.6, 6 males) and all were included in the analysis. Experiment 3 tested the spinal excitability during the different components of movement in the FDI of the right hand using F-waves. *Figure 2.4* displays the group means (with standard error of the mean) for each movement component. The repeated measures ANOVA revealed a significant main effect of PHASE ($F_{(3,18)} = 29.895$, $p < 0.0001$). Tukey's post hoc analysis revealed that there were significant differences between F-waves during rest versus phasic ($p < 0.0001$), rest versus tonic ($p = 0.03$), pre-movement versus phasic ($p < 0.0001$), pre-movement versus tonic ($p = 0.04$), but phasic versus tonic only approached significance ($p = 0.09$). These data indicate that, compared to rest, spinal excitability was increased during movement but not during the preparation to move.

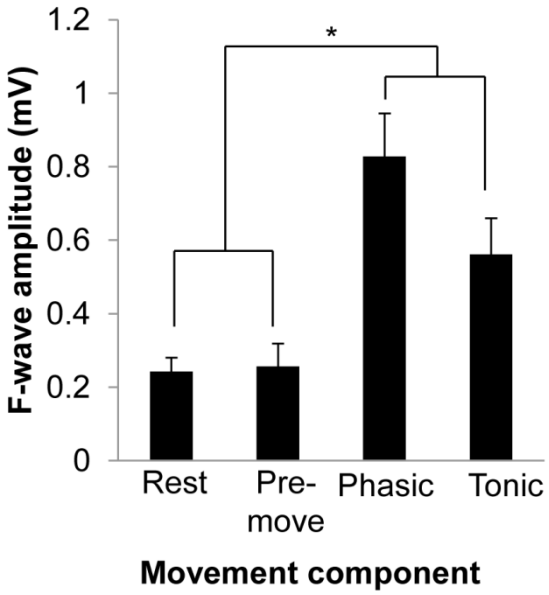

Figure 2.4. F-wave amplitude during different movement components in the index finger flexion task. Group-averaged data (with standard error of the mean) for each component of movement. The asterisk over the bar connecting the movement phases to rest and pre-movement conditions indicates that F-wave amplitude in both movement phases were significantly different than rest and pre-movement. Significant differences were tested at $p \leq 0.05$.

2.5.5 Experiment 4: Mixed nerve SAI with TMS at 1.2 RMT

This experiment tested whether SAI was altered during the different components of the movement using median nerve stimulation and a TMS intensity of 1.2 RMT. Using a 1.2 RMT normalization is technically easier to obtain across the movement components, but the problem with this approach is that the corticospinal excitability might be altered

across the movement components and could potentially confound the SAI results. Three people did not show SAI at rest and were excluded from the analysis. Nine subjects were therefore included in these results ($\bar{X}_{age}$ = 28.7, SD = 5.7, 4 females). The average percentage of maximal stimulator output for the group at 1.2 RMT was 45%. Mean 10% F_{max} was 4.18 N $\pm$ 0.46. *Figure 2.5* displays the group-averaged mean (with standard error of the mean) for each movement component. Repeated measures ANOVA revealed a significant main effect of PHASE ($F_{(3,24)} = 21.20$, $p < 0.0001$). *A priori* paired comparisons revealed that, compared to rest, SAI was reduced in all components of movement (pre-movement $p = 0.008$, phasic $p < 0.0001$, tonic $p = 0.001$). Further, SAI was significantly reduced during the phasic and tonic components compared to the pre-movement phase (phasic $p = 0.006$, tonic $p = 0.017$). In addition, to test for the presence of SAI during each movement component, paired comparisons revealed its existence during pre-movement ($p = 0.004$), but not during phasic ($p = 0.99$) and tonic ($p = 0.15$) components. Last, to test for differences in the amplitude of the unconditioned MEPs, the repeated measures ANOVA revealed a significant effect of PHASE ($F_{(3,24)} = 47.52$, $p < 0.0001$). Tukey's post hoc analysis revealed significant differences between rest versus phasic ($p < 0.0001$), rest versus tonic ($p < 0.0001$), pre-movement versus phasic ($p = 0.001$), and pre-movement versus tonic ($p = 0.003$). To test whether the magnitude of the unconditioned MEP amplitudes affected the degree of SAI, a Pearson's correlation coefficient was performed on the averaged unconditioned MEP amplitude and degree of SAI for each participant. This analysis revealed a significant correlation ($r = 0.64$, $p < 0.0001$) indicating that as the size of the unconditioned amplitude increased, SAI was

concurrently reduced. In summary, SAI was reduced during all movement components compared to rest, similar to the results in Experiment 1 using a ~ 1 mV normalization procedure. However, the reduction in SAI across the movement components may have been confounded by the increase in unconditioned MEP size during the phasic and tonic components of the movement.

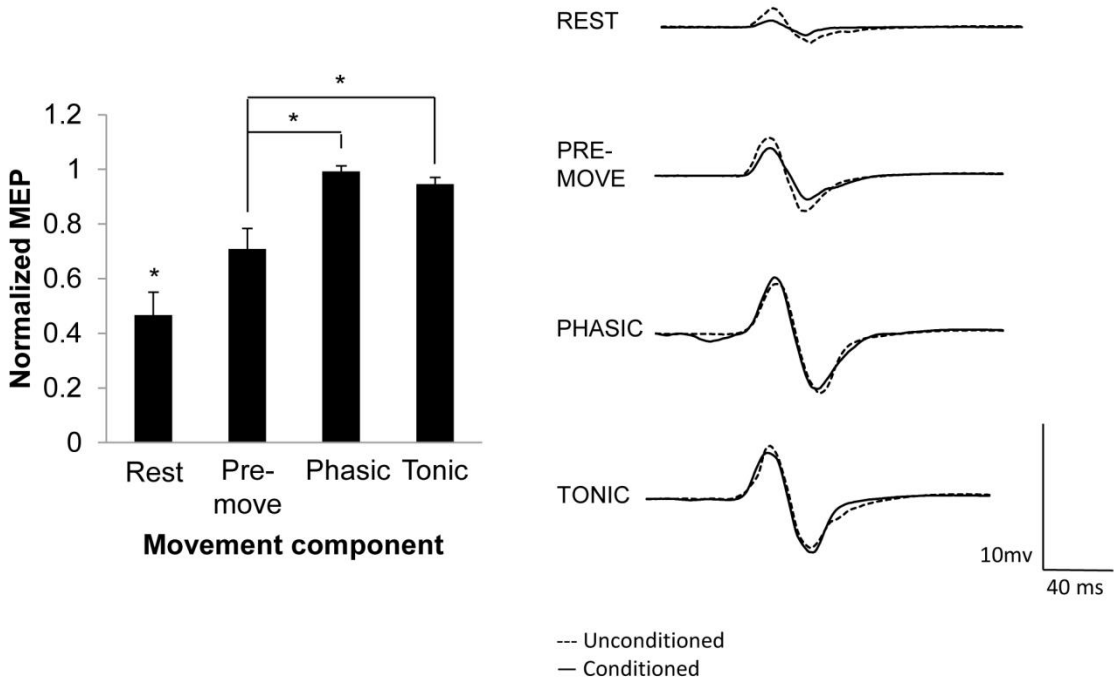

Figure 2.5. SAI induced by mixed nerve stimulation during different components of movement with TMS intensity at 1.2 RMT. Left: Group-averaged data (with standard error of the mean) for rest and each component of movement. Right: individual trial EMG traces from one participant demonstrating changes in SAI across task conditions. An asterisk over a single component of movement indicates it was significantly different than all other components of the movement. An asterisk over a bar connecting two components of movement indicates those components are significantly different. Significant differences were tested at $p \leq 0.05$.

2.6 Discussion

The present study investigated the modulation of SAI in the context of movement and identified somatic inputs that drive these alterations. SAI was measured during rest and during the pre-movement, phasic and tonic components of an index finger flexion reaction time task. We observed that SAI was decreased during all movement components compared to rest. The magnitude of SAI reduction was, however, dependent on the movement component and the nerve stimulated. The data suggest that increases in spinal excitability contribute to reduced SAI during movement while reductions in SAI prior to movement appear to be primarily cortically mediated.

SAI was reduced in all components of movement regardless of the nerve being stimulated. Reduction in SAI has been shown during the phasic and tonic component for the digital nerve [11,23,24] and in the tonic component for the mixed nerve [13]. In our study SAI was reduced in the phasic, tonic and also the pre-movement component for both types of submodal inputs. Specifically, SAI was reduced in the phasic component of movement by 27% similar to the ~25-30% reduction shown elsewhere [23]. Further, SAI was reduced by 30% during tonic contraction, similar to previous reports using median nerve stimulation [13], but less than the 50% reduction in SAI observed for digital nerve stimulation in past research [11]. The latter difference may relate to specific movement such that the 1st and 5th digit performed the tonic contraction [11].

There are several mechanisms that could mediate the reduction in SAI during the phasic and tonic components of movement. At rest, SAI is reduced with administration of $GABA_A$ agonist lorazepam, suggesting that GABAergic inhibitory interneurons are mediating this reduction [16–18]. During movement, reduced SAI may also be mediated by somatosensory afferent gating within S1 or sub-cortical loci that would result in less inhibition in M1. For example, during muscle contraction, SEPs are gated in the tonic component of movement compared to rest and further gated during EMG onset [29]. Our SAI data showed the same trend. Compared to rest, SAI was reduced in the tonic component and the reduction was even greater during the phasic component. Therefore, it appears that the magnitude of SAI may be related to the amplitude of SEPs such that an increase in SAI (i.e., more inhibition) may evoke concomitant increases in SEP amplitude (i.e. less gating), which indicates an increase in activity within S1.

Changes in spinal excitability may also account for reduced SAI during movement. Spinal excitability is increased during phasic and tonic components of movement [23,24,39,40] and we observed the same result. At rest, summation of three I-waves are needed to produce a MEP from a TMS pulse, while only the I1 wave is necessary to create a MEP during low voluntary contraction due to increased spinal excitability [34]. Since short-latency somatosensory input does not affect the I1 wave [8], the increased spinal excitability during the phasic and tonic components would allow the unaffected I1 wave to contribute to the MEP and yield reduced SAI in relation to rest. This evidence does not rule out the fact that the cortex may also contribute to reduced SAI during

movement, as the number of I-waves produced during voluntary contraction increases [41]. However, the amplitude of I-waves are unaltered at 20% MVC [41], a similar force level used in the present study, therefore we suggest that increases in spinal excitability are largely contributing to the reduction in SAI during movement. One behavioural reason for the increase in spinal excitability may be to reduce the inhibitory effects of short-latency somatosensory input on M1 because such inhibition may interfere with the ongoing movement. In support of this suggestion SAI is reduced in muscles involved in the movement but is increased in muscles not involved [23].

An important and novel finding was the reduction of SAI in the pre-movement component, which occurs without changes in spinal excitability. Past research has indicated that SICI is reduced during the delay period between the 'warning' and 'go' cue in a choice reaction time task [26,27] although SICI represents different inhibitory circuitry [16–20]. One mechanism for reduced SAI during the pre-movement component may relate to SEP gating as seen in monkeys during the delay period between a 'warning' and 'go' cue [28]. SEPs during the pre-movement component are reduced in M1 but unchanged at the level of the spinal cord or S1 [28]. These data suggest that reduced SAI in the pre-movement component may be due to somatosensory input providing less inhibition on M1 corticospinal output, indicating a cortical origin of the reduced SAI in this movement component. The evidence from our study does not exclude the possibility that increases in spinal excitability may contribute to reduced SAI since F-waves may not represent the same pool of spinal motorneurons recruited by a TMS pulse [42]. However,

our data suggest that reduced SAI in the pre-movement component is largely cortically mediated since F-waves remained unchanged. Specifically, it has been suggested that alterations in I3 wave can mediate large non-linear changes in MEP amplitude and we suggest that increases in this I wave created the observed differences in pre-movement SAI with minimal or no changes in spinal excitability [43].

There were similarities and differences in the degree of SAI evoked with cutaneous versus mixed nerve stimulation. The degree of SAI observed during rest was consistent with past studies using mixed [8,10,20,22,44,45] and cutaneous [8,23,24] nerve stimulation. When comparing nerves, we observed an ~ 35% increase in SAI for the mixed in relation to cutaneous nerve evoked SAI at rest. Increased SAI in the mixed versus cutaneous nerve has been observed in some instances [46] but not others [8]. We observed that SAI magnitude was greater in the pre-movement and tonic components for the mixed compared to cutaneous nerve, but the difference between nerves disappeared in the phasic component. This finding is different from a previous study demonstrating that SAI reduces MEPs by ~ 50 % for both the digital and median nerve stimulation during tonic contraction [8]. However, the latter difference may relate to the fact that the cutaneous nerve of both the 2^{nd} and 3^{rd} digit was stimulated [8]. The varying composition and volume of afferents recruited following stimulation of the median versus digital nerve may account for differences in SAI observed during rest and movement. Specifically, the larger volume of afferent input from the mixed nerve may have been driving the differences in SAI between the three movement components (rest, pre-movement, tonic).

However, it does not account for the lack of difference between the nerves in the phasic component. One possibility is that nerve-specific differences in SAI depend on the relevancy of the afferent input to the ongoing movement though further research needs to explore this issue.

We tested whether the same results of movement-related modulation of SAI could occur when using a technically easier methodology of obtaining TMS intensities. Past research has used a standardized TMS output based on RMT for comparison of SAI during movement [13,23,24]. In the present study, we compared unconditioned MEPs evoked using a TMS intensity of 1.2 RMT and a TMS intensity normalized to produce ~ 1 mV for each movement component. One disadvantage of using a standardized 1.2 RMT across all components of movement is that corticospinal excitability may be substantially different during movement (i.e., phasic, tonic) due to voluntary contraction [47]. We demonstrate that both approaches yield similar effects and suggest that a standardized TMS intensity is suitable for comparing SAI during movement to rest. However, when measuring subtle differences across movement components the two approaches yielded slightly different results. Specifically, there was more SAI in the tonic component for the ~ 1 mV normalization. Additionally, MEP amplitudes during movement with a standardized TMS intensity based on RMT confounded the SAI results, as with this methodology greater reduction of SAI correlated with larger MEP amplitudes. We therefore suggest a TMS output based on a ~ 1 mV normalization is a more suitable

approach when comparing subtle differences across movement components compared to a normalization based on RMT as used elsewhere [13,23,24].

Somatosensory input is crucial for performing precise movements with the arm and hand. Inputs from the periphery can modulate corticospinal excitability depending on the time course of the input [20,46], whether the inputs are natural [48] or electric [8], relevant to performing [49] and initiating a task [50–52] and following 40 minutes of repetitive ulnar nerve stimulation [53]. Our study is the first to compare SAI across different movement components and supports these previous findings such that short-latency somatosensory input from the periphery is modulated differently before and during movement and may be dependent on the composition or volume of afferent input carried by the stimulated nerve. This work may be applicable to certain movement disorders. SAI is altered in Parkinson's disease [54], in individuals with cerebellar symptoms [55], and after 1 Hz rTMS over S1 in Writer's cramps [56]. SAI has also been shown to correlate with functional recovery from stroke such that a reduction in SAI is indicative of positive functional outcome [25]. It is evident that altered SAI is present in a number of movement disorders, but all of the aforementioned studies tested SAI at rest. Future studies in clinical populations may investigate the modulation of SAI during different components of movement to determine if ineffective SAI modulation is one factor contributing to motor symptoms.

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2.8 Bridge to Study 2

In study 1, I determined that SAI is modified during movement and this modulation may have cortical origins. Further, SAI modulation is dependent on the nerve being stimulated or even the specificity of the nerves input to the task demands. The effects that were found in study 1 were only studied in a muscle that was involved in performing a task. When humans perform movements, it is important to activate muscles to perform a task, but it is equally important to inhibit activity to muscles that are not involved in the task or would interfere with the ongoing movement. One theory of the neurophysiology behind movement control is known as 'surround inhibition' and suggests that M1, along with other supraspinal structures, have the ability to reduce cortical output to muscles that are not involved in the task. SAI creates a transient inhibition of M1 via somatosensory input. It could be that SAI has the ability to inhibit output to muscles that are not involved in the task, but modify output to muscles involved in the task. In study 2, I sought to determine if SAI is modulated differently when a muscle is involved versus uninvolved in a task and if this modulation depends on which digit is performing the task and the movement phase.

3.0 Chapter 3: Modulation of short-latency afferent inhibition prior to movement depends on digit and task-relevance

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3.1 Abstract

Short-latency afferent inhibition (SAI) occurs when a single transcranial magnetic stimulation (TMS) pulse delivered over the primary motor cortex is preceded by peripheral electrical nerve stimulation at a short inter-stimulus interval (~20-28ms). SAI has been extensively examined at rest, but few studies have examined how this circuit functions in the context of performing a motor task. The present study investigated SAI in a muscle involved, versus uninvolved, in a motor task and, specifically, during three pre-movement phases; two movement preparation phases between a 'warning' and 'go' cue and one movement initiation phase between a 'go' cue and EMG onset. SAI was tested in the first dorsal interosseous (FDI) and abductor digiti minimi (ADM) muscles in twelve individuals. In a second experiment, the origin of SAI modulation was investigated by measuring H-reflex amplitudes from FDI and ADM during the motor task. The data indicated that changes in SAI occurred predominantly in the movement initiation phase during which SAI modulation depended on the specific digit involved in the task. Specifically, the greatest reduction in SAI occurred when FDI was involved in the task. In contrast, these effects were not present in ADM. Changes in SAI were primarily mediated via supraspinal mechanisms during movement preparation, while both supraspinal and spinal mechanisms contributed to SAI reduction during movement initiation.

3.2 Introduction

Short-latency afferent inhibition (SAI) occurs when a single transcranial magnetic stimulation (TMS) pulse over the primary motor cortex (M1) is preceded by peripheral electrical nerve stimulation at a short inter-stimulus interval (i.e., ~20-28 ms) such that the corticospinal output to the targeted hand muscle is reduced [1,2]. The functional significance of SAI to hand control remains largely unknown yet movement of a muscle can modify the magnitude of SAI [3,4]. We and others have shown that SAI is reduced during both the onset of muscle activity [3,5,6] and during sustained muscle contraction [3,4]. Specifically, we observed reductions in SAI as early as movement preparation between an auditory 'warning' and 'go' cue and these reductions are likely cortically or sub-cortically mediated [3]. However, a number of questions regarding the functional significance of SAI remain unexplored. First, how is SAI modified when the muscle is involved versus uninvolved in the task? [5,6]. Second, does the modulation of SAI depend on the specific digit (i.e., digit 2 versus digit 5)? Each digit contributes differently to the functional capacity of the hand such that the amputation of the 2^{nd} versus 5^{th} digit results in a 20% and 10% loss in overall hand function, respectively [7]. It may be that SAI is involved in focussing neural activity differently depending on the specific digit that is or is uninvolved in the task.

The purpose of this study was to determine whether SAI is modulated during movement preparation (i.e., between a 'warning' and 'go' cue) and movement initiation (i.e., between a 'go' cue and onset of muscle activity) when a muscle is involved or uninvolved

in a finger flexion task. SAI was measured in the first dorsal interosseous (FDI) and abductor digiti minimi (ADM) to represent muscles controlling the 2nd and 5th digit, respectively, which contribute differently to the overall functional capacity of the hand. In a second experiment, spinal excitability via the Hoffman reflex (H-reflex) was measured in FDI and ADM during the same motor task.

3.3 Methods

3.3.1 Ethics Statement

This study was approved by the Office of Research Ethics at McMaster University and conformed to the *Declaration of Helsinki*. Written informed consent was obtained from all participants in the study.

3.3.2 Participants

Twelve healthy individuals ($\bar{X}_{age}$ = 20, SD = 2, 5 females) participated in Experiment 1 and of those, ten subjects ($\bar{X}_{age}$ = 20.1, SD = 2.1, 6 males) participated in Experiment 2. All participants were deemed to be right handed determined using a modified version of the Edinburgh Handedness Inventory [8]. All participants were screened for any contra-indicators of TMS (i.e., no intake of benzodiazepines).

3.3.3 Electromyography (EMG)

Surface Ag/AgCl EMG electrodes were placed on the FDI and ADM muscles of the right and left hands in a muscle belly-tendon montage. The right hand was engaged in the task while the left hand remained relaxed throughout the experiments. The analog signal from the electrodes was amplified with a gain of 1000, band-pass filtered between 20 and 2500 Hz (Intronix Technologies Corporation Model 2024F, Bolton, Canada) and sampled at a frequency of 5000 Hz using an analog-to-digital interface (Power 1401, Cambridge Electronic Design, Cambridge, UK). The EMG electrodes were used to measure the peak-to-peak amplitude of the MEP elicited in the FDI and ADM of the right hand and ongoing EMG activity of the FDI and ADM in the relaxed left hand. Analysis was completed off-line using Signal software (version 5.07, Cambridge Electronic Design, Cambridge, UK).

3.3.4 Peripheral Nerve Stimulation

Peripheral nerve stimulation was achieved with 200 μs square wave pulses delivered using Grass SD9 Telefactor stimulators (Grass Technologies, West Warwick, USA). The digital nerves of the 2^{nd} and 5^{th} digits were stimulated using ring electrodes with the cathode proximal to the anode and positioned around the proximal and intermediate phalynx. Digital nerves were stimulated at ~ 3 times perceptual threshold, an intensity shown to evoke SAI at rest [1]. To elicit H-reflexes, the ulnar nerve was stimulated (1 ms square wave pulse) at the wrist approximately 8 cm proximal to the thenar muscles of the right hand. The intensity of ulnar nerve stimulation was set to elicit M-waves of 10% of

the direct maximal muscular response (M-wave$_{max}$) in FDI or ADM. This intensity was used to ensure the H-reflex recorded was on the ascending portion of the H-reflex recruitment curve [9]

3.3.5 Transcranial Magnetic Stimulation (TMS)

TMS was delivered using two custom built 50 mm diameter figure-of-eight branding coils connected to two Magstim 200^2 stimulators (Magstim, Whitland, UK). Coil position and orientation was monitored throughout the experiment using Brainsight Neuronavigation (Rogue Research, Montreal, Canada) with optical sensors placed on the coil and the participant. The coil was oriented at 45° in relation to the parasagittal plane to induce a posterior-lateral to anterior-medial current in the cortex and preferentially activate corticospinal neurons trans-synaptically [10]. One TMS coil delivered a monophasic pulse over M1 in the optimal location to elicit MEPs in the FDI muscle of the right hand, while a separate coil delivered a monophasic pulse over the optimal location to elicit MEPs in the ADM muscle of the right hand. The optimal hotspot for each muscle was obtained separately and was determined by the position of the coil that produced a MEP ~1 mV at the lowest percentage of maximal stimulator output (%MSO). The hotspot for FDI was first identified and subsequently the ADM hotspot was located. The group-averaged difference between ADM hotspot in relation to the FDI hotspot was 3 mm medial and 7 mm posterior.

3.3.6 Behavioural task

A similar behavioural task was performed in Experiments 1 and 2. At the beginning of the set-up, participants were seated with their right arm relaxed with their shoulder abducted ~ 20° and elbow flexed at ~ 90°. In this position, participants voluntarily flexed their finger at the metacarpophalangeal joint maximally against a load cell (Transducer Techniques, model THA-50-Q load cell). This measure was completed for the 2^{nd} and 5^{th} digits separately. Participants then practiced performing a phasic isometric finger flexion to 5% of their maximum force (F_{max}) for their 2^{nd} and 5^{th} digit (5% F_{max}), separately, using visual feedback of their force displayed on an oscilloscope. The 5% F_{max} was the force requirement for the behavioural task.

Each trial consisted of an auditory tone that served as the 'warning' cue followed 2 to 3 seconds later by a second auditory tone that served as the 'go' cue (*Figure 3.1*). The 'warning' cue dictated which action to perform: a high frequency tone indicated 2^{nd} digit movement, while a low frequency tone indicated 5^{th} digit movement. The meaning of the tone was counterbalanced across participants. Upon hearing the 'go' cue, participants flexed their 2^{nd} or 5^{th} digit to 5% F_{max} against a load cell and released the contraction once 5% F_{max} was achieved (i.e., a phasic contraction). The voltage from the load cell was passed through a strain gage amplifier (Futek model CSG110-FSH03546, Thornhill, Canada) and the online force level achieved by the 2^{nd} or 5^{th} digit was displayed on an oscilloscope as a bright line. Subjects were required to position one line which

represented their current force level over another line that marked the 5% F_{max} for that particular digit.

3.3.7 Experiment 1: SAI in FDI and ADM

SAI was investigated in FDI and ADM by placing the coil on the motor hot spot for each respective muscle. To elicit SAI in FDI or ADM, stimulation was applied to the digital nerve of the 2nd or 5th digit, respectively. SAI in these muscles was investigated during three pre-movement phases prior to EMG onset such that a single TMS pulse was delivered either 100 ms after the 'warning' cue in the post-warning 1 phase (PW1) (*Figure 3.1*), 1000 ms after the 'warning' cue in the post-warning 2 phase (PW2), or 100 ms after the 'go' cue in the post-go phase (PG). Any trial in which participants anticipated the 'go' cue (EMG at or before 100 ms) was rejected offline and not included in the analysis. SAI was tested in each muscle (FDI, ADM) and at each time point (PW1, PW2, PG), while the participant was in the context of performing either 2nd or 5th digit movement dictated by the tone frequency. Twelve conditions were tested in total: 3 pre-movement phases (PW1, PW2, PG) x 2 types of movement (2nd, 5th digit flexion) x SAI in 2 muscles (ADM, FDI). Twenty trials were completed for each condition whereby ten trials delivered a single TMS pulse only (i.e., unconditioned MEP) and the other ten delivered stimulation to the appropriate digital nerve 25 ms prior to the TMS pulse to evoke SAI (i.e., conditioned MEP) [4]. The order of conditioned and unconditioned MEPs was randomized. For FDI and ADM, the stimulator output was adjusted to elicit an unconditioned MEP of ~1 mV from a single TMS pulse in each of PW1, PW2 and PG,

while the participant was preparing to perform either 2nd or 5th digit movement. The reason for adjusting the stimulator output for each condition is that the TMS intensity to elicit an MEP of ~1 mV in the targeted muscle might be different for preparation of 2nd versus 5th digit movement. Further, when the muscle is involved or uninvolved in the task, the MEP could be increased or reduced, respectively, and the differing amplitude of the unconditioned MEP can affect the degree of SAI [4]. Therefore, the group-averaged %MSO for each condition is presented in Table 1. Each of the 12 conditions were performed in separate blocks. The inter-trial interval varied between 4 and 5 seconds. Additionally in a block, no stimulation trials (i.e., no TMS or nerve stimulation) and dummy trials (i.e., required to move 5th digit when SAI is being tested during a 2nd digit movement) were included to avoid the participant predicting the trial type being tested in the block and prevent any anticipation effects of TMS or nerve stimulation. The block order was randomized across participants. In addition to the pre-movement trials, rest trials were performed whereby participants were required to relax their hand completely. Twenty resting trials were completed; ten unconditioned and ten conditioned MEPs, and split up into two blocks for each muscle (i.e., 4 blocks total). The rest blocks were either performed before and in the middle of the testing blocks or in the middle and the end of the testing blocks.

For all pre-movement phases and rest trials, the experimenter rejected any trials offline whereby EMG had a peak-to-peak amplitude > 20 μV over the resting background EMG signal 200 ms before the TMS pulse, similar to previous work [6]. If crossing this

threshold was indicated during a trial, it was rejected online and the trial was repeated. If the threshold of EMG activity could not be detected online, the trial was rejected offline during data analysis.

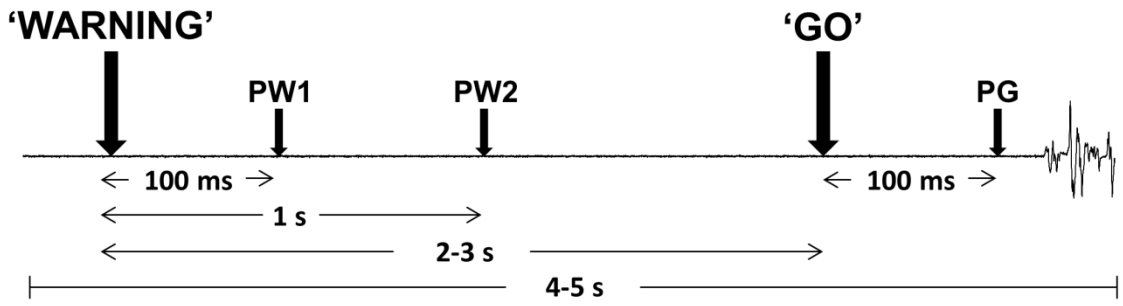

Figure 3.1. Task conditions. Trial timeline of the PW1, PW2, PG, and no stimulation conditions. The 'Warn' and 'Go' represent the 'warning' and 'go' cue, respectively. The 'warning' cue defined whether to perform 2nd or 5th digit movement. '100 ms' on the left side of the timeline represents the time between the 'warning' cue and when SAI was tested in the post-warning 1 phase (PW1). '1 s' represents the time between the 'warning' cue and when SAI was tested in the post-warning 2 phase (PW2). '100 ms' on the right side of the timeline represents the time between 'go' cue and when SAI was tested in the post-go phase (PG). '2-3 s' is the varied interval between the 'warning' and 'go' cue, while the '4-5 s' indicate the varied length of the trial. In the 'no stimulation' condition, neither TMS nor nerve stimulation was delivered, but the participant still completed the trial with the 'warning' and 'go' cue present.

Table 3.1. Percentage of MSO to obtain ~1mv MEP in each condition.

	Rest	Move 2nd digit			Move 5th digit		
		PW1	PW2	PG	PW1	PW2	PG
FDI	51 ± 3	52 ± 3	51 ± 3	47 ± 4	53 ± 3	53 ± 4	55 ± 4
ADM	60 ± 3	61 ± 4	61 ± 5	61 ± 4	61 ± 5	60 ± 4	53 ± 4

Means (% MSO) followed by standard error are presented

3.3.8 Experiment 2: Spinal excitability measured with H-reflex

H-reflexes were used to investigate whether SAI modulation may occur via spinal and/or supraspinal mechanisms [11]. The H-reflex measure was used to determine if spinal excitability changes as a function of phase, muscle and task involvement. H-reflexes were obtained in FDI or ADM by having the participants produce a light voluntary contraction with their 2nd or 5th digit, respectively. This stimulus duration and light voluntary contraction was implemented because an H-reflex is more readily obtained in FDI and ADM when they are slightly active [12]. Participants performed the same behavioural task as in Experiment 1 (12 testing conditions with dummy and no stimulation trials and one rest condition) with one exception for all conditions. The participant maintained a light voluntary contraction in the digit that the targeted muscle for the H-reflex was actively involved in (e.g., 2nd digit for FDI or 5th digit for ADM H-reflex) and increased the force by ~5% in response to the 'Go' cue. The force requirement during the task was the same for 2nd and 5th digit.

3.4 Statistical analyses

SAI was calculated as the ratio of the conditioned MEP to the unconditioned MEP ($SAI = \frac{PNS,TMS}{TMS_{alone}}$). Spinal excitability was defined with the following formula using the peak-to-peak amplitude of the H-reflex and M-wave: $Spinal\ Excitability = \frac{H-reflex}{M-wave\ max}$. A three-way repeated measures ANOVA with factors PHASE (3 levels:

PW1, PW2, PG), MUSCLE (2 levels: FDI, ADM), and MOVEMENT TYPE (2 levels: 2nd, 5th digit) was conducted for SAI (Experiment 1) and spinal excitability (Experiment 2). For both ANOVAs the dependent measures of SAI and spinal excitability were normalized to the measure at rest (i.e., $SAI_{ratio} = \frac{SAI_{phase}}{SAI_{rest}}$; $Spinal\ Excitability_{ratio} = \frac{Spinal\ Excitability_{phase}}{Spinal\ Excitability_{rest}}$). This normalization allows for the comparison of increases or decreases of SAI or spinal excitability between muscles (e.g., SAI reduction in FDI in relation to SAI reduction in ADM). Means less than 1 indicate increased SAI (or decreased spinal excitability) in relation to rest and means greater than 1 indicate reduced SAI (or increased spinal excitability) in relation to rest. Tukey's post-hoc analysis was performed if a significant effect was found.

Second, we tested whether there was a relationship between unconditioned MEP amplitude and degree of SAI. The reason for this analysis was to ensure that the unconditioned MEP amplitude did not affect the degree of SAI, as larger MEP amplitude could potentially yield reduced SAI [4]. Pearson's product moment correlation coefficient between the unconditioned MEP amplitude (i.e., TMS_{alone}) and the degree of SAI ($SAI = \frac{PNS,TMS}{TMS_{alone}}$) in each muscle during both 2nd and 5th digit movement [3].

For all statistical tests, the alpha level was set at $p \leq 0.05$. Sphericity was tested and when this assumption was violated the Greenhouse Geisser correction was implemented and the adjusted degrees of freedom were reported.

3.5 Results

3.5.1 Experiment 1: SAI during pre-movement

Experiment 1 examined whether SAI was dependent on the specific digit and its involvement in the task being performed. The group mean F_{max} for the 2nd digit was 30.9 N $\pm$ 11.5 and 18.5 $\pm$ 6.9 for the 5th digit similar to previous research [3]. *Figure 3.2* displays the group-averaged SAI ratio (with standard error of the mean) during the pre-movement phases (PW1, PW2, PG) for each muscle (FDI, ADM) and each task (involved, uninvolved). The repeated measures ANOVA revealed a significant three-way interaction between PHASE, MOVEMENT TYPE, and MUSCLE ($F_{(1.3,14.4)} = 4.803$, $p = 0.037$), a PHASE by MOVEMENT interaction ($F_{(2,22)} = 5.238$, $p = 0.024$), and main effect of PHASE ($F_{(2,22)} = 4.069$, $p = 0.031$) and MUSCLE ($F_{(1,11)} = 19.520$, $p = 0.001$). Post-hoc Tukey's test revealed effects in the PG phase. For the task involvement effect, post-hoc Tukey's test revealed that SAI is reduced in FDI when it was involved versus uninvolved in the task during movement initiation ($p < 0.05$). However, there were no differences of SAI in ADM when it was involved versus uninvolved in the task. To examine the muscle specific effects, post-hoc Tukey's revealed that SAI in FDI was significantly reduced compared to ADM when each muscle was involved in the task. There were no differences in SAI between FDI and ADM when there were uninvolved in the task. These data indicate that SAI reductions are task and muscle specific. Table 2 indicates the group means (with standard error of the mean) for the SAI ratio data during rest and the pre-movement phases.

There was no significant correlation between the unconditioned MEP amplitude (i.e., TMS alone) and the magnitude of SAI ($SAI = \frac{PNS,TMS}{TMS_{alone}}$) in FDI during 2nd digit movement (r = -0.176, p = 0.23), FDI during 5th digit movement (r = -0.019, p = 0.896), ADM during 2nd digit movement (r = -0.108, p = 0.466), nor ADM during 5th digit movement (r = -0.148, p = 0.315), indicating that the changes in SAI were due to the movement phase and not MEP amplitude for every muscle in each type of movement.

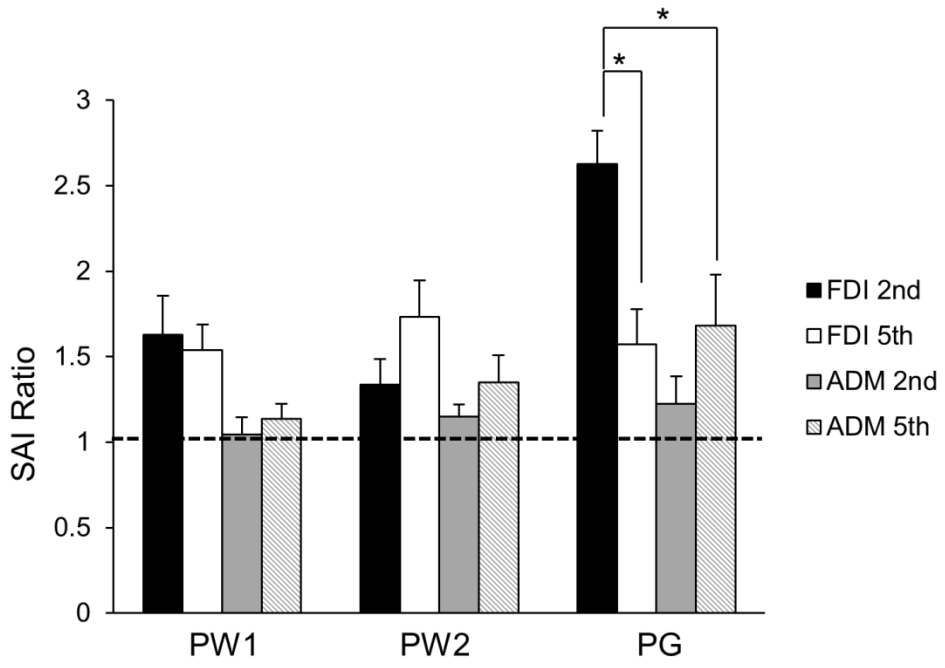

Figure 3.2. Differences in SAI across the three pre-movement phases. Group-averaged SAI ratio data (with standard error of the mean) for each pre-movement time point (i.e., PW1, PW2, PG) and muscle (FDI, ADM). Values greater than 1 indicate a reduction in SAI, while values less than 1 indicate an increase in SAI. An asterisk over a

bar connecting two different conditions indicates significant differences. Significant differences were tested at $p < 0.05$.

Table 3.2. SAI data and SAI ratio for FDI and ADM during all conditions.

		SAI Data						SAI Ratio Data					
Muscle	Rest	Move 2nd digit			Move 5th digit			Move 2nd digit			Move 5th digit		
		PW1	PW2	PG	PW1	PW2	PG	PW1	PW2	PG	PW1	PW2	PG
FDI	0.51 ± 0.053	0.80 ± 0.126	0.66 ± 0.087	1.32 ± 0.233	0.78 ± 0.104	0.87 ± 0.122	0.74 ± 0.064	1.63 ± 0.229	1.34 ± 0.195	2.63 ± 0.374	1.54 ± 0.152	1.73 ± 0.211	1.57 ± 0.208
ADM	0.68 ± 0.051	0.68 ± 0.06	0.77 ± 0.065	0.76 ± 0.057	0.75 ± 0.072	0.88 ± 0.105	1.14 ± 0.267	1.05 ± 0.101	1.15 ± 0.068	1.22 ± 0.163	1.13 ± 0.089	1.35 ± 0.161	1.68 ± 0.301

Means for SAI data ($SAI = \frac{PNS,TMS}{TMS_{alone}}$) and SAI ratio data $\left(SAI_{ratio} = \frac{SAI_{phase}}{SAI_{rest}}\right)$. HSD critical for a significance of 0.05 was calculated as 0.81 for comparing amongst SAI ratio data.

3.5.2 Experiment 2: H-reflex during pre-movement

Experiment 2 examined whether spinal excitability was dependent on the muscle involved and the task being performed. The group mean F_{max} for the 2nd digit was 23.7 N ± 10.7 and 15.5 ± 6.8 for the 5th digit. The repeated measures ANOVA revealed a significant 3-way interaction ($F_{(2,18)} = 7.085$, $p = 0.005$) across factors PHASE, MOVEMENT TYPE, and MUSCLE, and a significant main effect of PHASE ($F_{(2,18)} = 13.198$, $p < 0.001$). *Figure 3.3* displays the group-averaged means (with standard error of the mean) for spinal excitability ratio during the pre-movement phases (PW1, PW2, PG) for each muscle (FDI, ADM) and each task (involved, uninvolved). Similar to the SAI data, post-hoc Tukey's test revealed effects in the PG phase. Spinal excitability was larger in FDI when it was involved versus uninvolved in the movement ($p < 0.05$). Similarly, spinal excitability was larger in ADM when it was involved versus uninvolved in the movement ($p < 0.05$). There were no muscle specific effects observed between FDI and ADM. In summary, these data indicate that spinal excitability was increased

when each muscle was involved versus uninvolved in the task. Table 3 indicates the group means (with standard error of the mean) for all spinal excitability data.

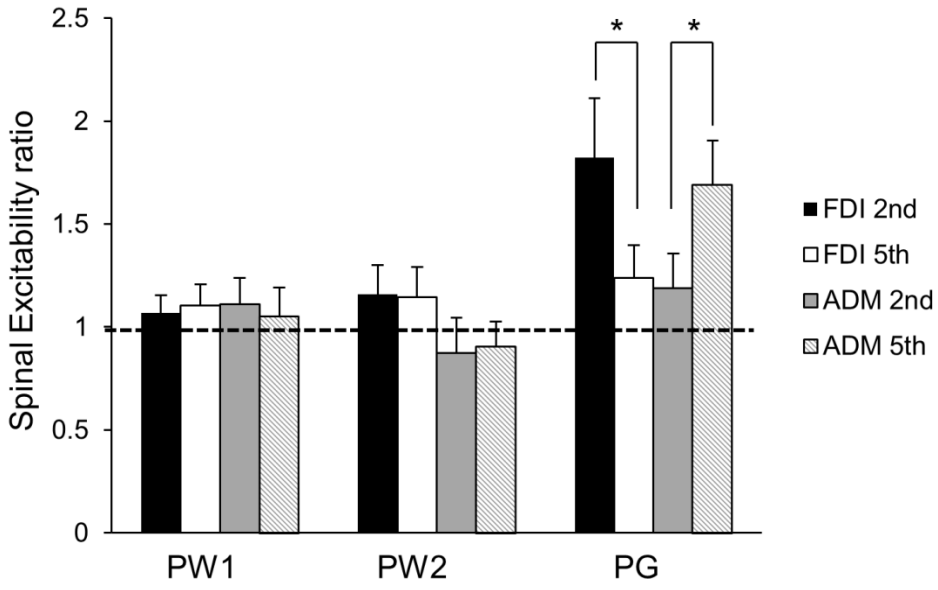

Figure 3.3. Differences in spinal excitability across the three pre-movement phases. Group-averaged spinal excitability data (with standard error of the mean) for each pre-movement time point (i.e., PW1, PW2, PG) and muscle (FDI, ADM). Values greater than 1 indicate an increase in spinal excitability, while values less than 1 indicate decreases in spinal excitability. An asterisk over a bar connecting two different conditions indicates significant differences. Significant differences were tested at $p < 0.05$.

Table 3.3. Spinal excitability data and spinal excitability ratio data for FDI and ADM during all conditions.

		Spinal Excitability Data						Spinal Excitability Ratio Data					
Muscle	Rest	Move 2nd digit			Move 5th digit			Move 2nd digit			Move 5th digit		
		PW1	PW2	PG	PW1	PW2	PG	PW1	PW2	PG	PW1	PW2	PG
FDI	0.01 ± 0.003	0.02 ± 0.003	0.02 ± 0.003	0.03 ± 0.009	0.02 ± 0.004	0.02 ± 0.005	0.02 ± 0.007	1.07 ± 0.088	1.16 ± 0.144	1.82 ± 0.288	0.04 ± 0.003	1.16 ± 0.144	1.24 ± 0.158
ADM	0.06 ± 0.016	0.05 ± 0.014	0.04 ± 0.007	0.06 ± 0.015	0.06 ± 0.020	0.04 ± 0.010	0.09 ± 0.020	1.11 ± 0.126	0.87 ± 0.171	1.19 ± 0.167	1.05 ± 0.139	0.90 ± 0.121	1.69 ± 0.215

Means for spinal excitability ($Spinal\ Excitability = \frac{H-reflex}{M-wave\ max}$) and spinal excitability ratio ($Spinal\ Excitability_{ratio} = \frac{Spinal\ Excitability_{phase}}{Spinal\ Excitability_{rest}}$) followed by standard error. HSD critical for a significance of 0.05 was calculated as 0.44 for comparison among spinal excitability ratio data.

3.6 Discussion

The goal of the present study was to investigate SAI in muscles involved and uninvolved in a finger flexion task and determine whether the degree of SAI modulation depended on the specific digit. We chose to study two digits, the 2nd and 5th, that contribute differently to whole hand function. Results indicated that SAI behaved differently in FDI compared to ADM. SAI in FDI was reduced when FDI was involved versus uninvolved in the task and this effect was observed only during movement initiation. In contrast, SAI in ADM was not modulated by its involvement in the task. Further, during movement initiation the reduction of SAI in FDI was greater compared to ADM when each muscle was involved in the task. In summary, SAI was modulated differently before movement onset for muscles controlling the 2nd versus 5th digit, primarily in the PG phase. The findings from this study are applicable to individuals with certain movement disorders and may provide insight into the direction of interventions for neurorehabilitation [6,11,13].

Mechanisms of SAI modulation

To determine whether increases in spinal excitability may contribute to SAI modulation, H-reflexes were recorded since this technique recruits the same motorneuron pool as that recruited from a single TMS pulse [12]. During movement initiation, there was an increase in spinal excitability in the specific muscle involved in performing the task (see *Figure 3.3*), but this effect was not present during movement preparation. Therefore, during movement preparation, changes in SAI may be mediated by supraspinal

mechanisms while changes in SAI during movement initiation appear to be mediated by both spinal and supraspinal mechanisms.

Although the supraspinal mechanisms, that may reduce SAI during movement preparation and movement initiation, are not well understood, several possibilities exist. One mechanism may involve an increase in GABAergic activity as $GABA_A$ agonist lorazepam reduces SAI at rest [14–16]. For example, the large reduction in SAI that we observed in FDI during 2nd digit movement may result from an interaction of GABAergic inhibitory interneurons or an interaction of different $GABA_A$ sub-unit inhibitory interneurons, both of which cause a large SAI reductions as shown previously [17,18]. One pathway for SAI modulation may involve the prefrontal cortex (PFC) and the thalamic reticular nucleus (TRN) [19,20]. The PFC has dense connectivity with the TRN and this connectivity has the ability to modify sensory input based on its relevancy to the task. It is possible that PFC and TRN connectivity may modify the inputs reaching cortex and ultimately, modify SAI during movement preparation and initiation. Although these proposed mechanisms are speculative, we believe that our results provide ground work for future studies to explore this mechanism using pharmaceutical interventions that can alter GABAergic activity. Irrespective of the precise mechanism involved in creating SAI reduction, this effect may be necessary to focus neural activity for the muscle involved in the task.

Digit specific effects of SAI

Amputation of the 2nd digit results in a greater loss of overall hand function in relation to the 5th digit [7], suggesting that the 2nd digit is more important to hand control. The 2nd digit also contributes more than the 5th digit during static grip [21], gripping an object with varying force levels [22], and during different gripping tasks [23], giving converging evidence of the superior importance of the 2nd digit to hand function. We observed effects of SAI modulation that were stronger for FDI compared to ADM, which are muscles controlling the 2nd and 5th digit, respectively. Since the 2nd digit contributes more to hand function, one speculation is that this difference would allow a larger proportion of neurons representing the 2nd digit within the primary somatosensory cortex (S1) to project to M1 and drive the greater modulation of SAI for a muscle controlling the 2nd digit observed in this study. In support of this statement, the cortical representation of the 2nd digit may be larger than the 5th digit [24], potentially because of its greater involved in hand control [25–27].

Functional significance of SAI modulation

SAI creates a transient inhibition of M1 shortly after stimulation of a peripheral nerve and this inhibition might function to focus the neural activity in M1 during movement initiation. Similar to SAI, surround inhibition is a neurophysiological mechanism that inhibits surrounding muscle representations that are not performing the desired movement. Past reports on surround inhibition state that this neurophysiological mechanism is most prominent during movement initiation [11,28] and it is during this phase that we observed the most robust modulation of SAI across task and muscles.

When FDI was performing the task, there was the greatest reduction in SAI. This reduction may be necessary to allow somatosensory input to increase activity in the area of M1 responsible for the desired motor output. Conversely, there was a lesser degree of SAI reduction when the digit was uninvolved in the task, particularly for FDI, and this level of SAI may be necessary to prevent unwanted movements. Overall, the data suggests that SAI may function to inhibit or focus neural activity during movement initiation even before the onset of muscle activity.

Applications to movement disorders

In certain movement disorders such as focal hand dystonia (FHD), digit representations in S1 overlap [29,30]. Further, in typically functioning adults, stimulation of multiple digits reduces the amount of inhibition within M1 in relation to single digit stimulation [31]. In FHD where digit representations overlap in S1, stimulation of a single digit during movement initiation could activate other digit representations in the cortex and cause a reduction in SAI across multiple muscles leading to unwanted movements of other digits. In FHD there is also lack of surround inhibition [11,28] and maladaptive modulation of SAI may be adding to problems in this network. To support this statement, individuals with Parkinson's disease who also present with unwanted movements exhibit facilitation instead of SAI when a digit in the surrounding area is stimulated [32]. Further, a reduction in SAI is correlated with functional recovery from stroke with larger reductions in SAI being associated with more movement [33]. As a result, how SAI is modulated

during movement initiation for muscles involved versus uninvolved in a task may be a marker for certain movement disorders that present with unwanted movements.

Limitations

There are a few limitations that may impact our interpretation of the data. We recorded H-reflexes to determine the level of spinal excitability in each muscle during the phases of movement. When measuring spinal excitability in FDI by stimulating the ulnar nerve, heteronymous excitation of the median nerve is possible [34] and could activate the first lumbrical muscle. A future study to test whether the type of nerve innervating the digit drives this SAI modulation may compare movements of a muscle in the thumb such as abductor pollicis brevis (i.e., median nerve) versus ADM (i.e., ulnar nerve). Last, we added light voluntary contraction when recording H-reflexes since this approach was necessary to record reflexes from these hand muscles and therefore, there was a small increase in force level to perform this task. Evidence in a study on lower limb spinal excitability, however, indicates that small increases in overall MVC does not affect H-reflex amplitude [35]. Thus, it is unlikely that the force level modification in the present work affected spinal excitability.

Conclusion

SAI modulation prior to the onset of movement behaved differently for muscles controlling the 2^{nd} versus 5^{th} digit and how they differed depended on the movement phase tested. This work on the functionality of SAI has implications to individuals with

certain movement disorders such as focal hand dystonia and Parkinson's disease that have difficulties preventing unwanted movements. Interventions aimed at improving SAI modulation during wanted and unwanted movements may improve hand function in certain movement disorders.

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The authors declare no conflict of interest.

3.7 Reference List

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3.8 Bridge to Study 3

In study 1 and 2, I explored how SAI functions depending on the movement phase, nerve stimulated, the digit a muscle controls, and the involvement of the digit in the task. A plethora of research has studied how cortical circuits may contribute to hand control likely because of the important role direct projections from the cortex to alpha motorneurons have on muscles controlling the hand. What is less known is how cortical circuits contribute to the control of upper limb musculature. There is evidence to suggest that cortical circuits controlling the upper limb muscles behave similar to circuits that output to hand muscles. The sparse amount of research that has used TMS to study cortical control of upper limb muscles has studied the neural circuits while the muscle was maintained in a 'resting' state. Further, it is difficult to understand how the cortex controls upper limb muscles during movement because of the complexity of multi-joint movements due to bone on bone forces/moments (i.e., how motion of one segments affects motions of other inter-connected segments). Therefore, it is important to understand how M1 output is modified depending on the mechanical interactions between connected segments during movement. Study 3 sought to determine how corticospinal output from M1 is modified depending on the mechanical interactions between segments during multi-joint movements.

4.0 Chapter 4: TMS induced corticospinal output is dependent on inertial and bone on bone contact moment contributions to joint rotation

Asmussen, M. J., Bailey, A.Z., & Nelson, A. J.

(Study 3, In Preparation)

4.1 Abstract

Performing multi-joint movements is inherently more complex in relation to single joint movements because of the forces that arise from inter-connected segments. This mechanical interaction between segments must be accounted for by the neural control signal. The present study investigated whether corticospinal output to upper arm muscles is influenced by the force that arises from inter-connected segments and contributes to shoulder and elbow joint motion, and whether surround inhibition may be an underlying mechanism that allows for these forces to contribute to joint motion. Participants reached to targets that inertia would aid in joint rotations or inertia would have to be overcome to perform the movement successfully. Further, these targets involved unique combinations of *resistive* and *assistive* bone on bone contact (BBC) moments. It was expected that corticospinal output to certain muscles would be dependent on the inertial contribution to joint rotation and the direction and magnitude of the BBC moment. Our study revealed that the inertial contributions to joint motion and BBC moments (i.e., *assistive* or *resistive*) modulates corticospinal output to muscles of the upper arm during a wide variety of complex multi-joint movements prior to, and during, movement. Further, the data suggest that surround inhibition may not exist during multi-joint movements and may not be a mechanism that allows humans to use inertia and BBC moments to their advantage to perform complex multi-joint movements. In sum, the activity within the primary motor cortex is dependent on the inertial and BBC moment contributions to joint motion during movement planning and execution of multi-joint actions.

4.2 Introduction

In our everyday lives, we perform multi-joint movements with complex mechanical interactions and these inter-segmental interactions must be accounted for by the neural control signal. Relative to single-joint movements, multi-joint movements are inherently more complex because of the motion created by reaction forces and moments acting at the joints of other inter-connected segments. Based on the configuration of the arm, inertia can either 'aid' to the intended joint rotation or have to be 'overcome' to produce joint rotation. Further, depending on its direction, the bone on bone force from one segment can create a moment about an inter-connected segment (i.e., a bone on bone contact (BBC) moment). Thus, it is difficult for the neural control signal to coordinate multi-joint movements because of inertial and BBC moment contributions to joint rotations.

The primary motor cortex (M1) is essential to the performance of complex multi-joint movements (Canedo, 1997; Scott, 2000; Scott, 2005). There is emerging evidence in humans to suggest that M1's output towards shoulder muscles encodes the effects of a torque applied to the elbow joint without any corresponding shoulder joint motion (Pruszynski et al., 2011). Further, inertial contributions and BBC moments modify M1 output such that motor evoked potentials (MEPs) from a transcranial magnetic stimulation (TMS) pulse increase when the inertia of the limb(s) and the BBC moments *resist* the intended joint rotation (Gritsenko, Kalaska, & Cisek, 2011). Inertial contributions to joint rotations and BBC moments are a reality during effective multi-joint movements (Dounskaia, Ketcham, & Stelmach, 2002; Dounskaia, 2005; Dounskaia,

Swinnen, Walter, Spaepen, & Verschueren, 1998; Goble, Zhang, Shimansky, Sharma, & Dounskaia, 2007) and the inability to use BBC moments for joint rotations may be a symptom of movement impairments in clinical populations (Bastian, Martin, Keating, & Thach, 1996; Bastian, Zackowski, & Thach, 2000; Sainburg, Ghilardi, Poizner, & Ghez, 1995; Asmussen, Przysucha, & Dounskaia, 2014). There also appears to be an economical benefit to the use of inertia and BBC moments in goal-directed movements such that when these contributions *assist* the intended joint rotation, there would be a reduction in the neural cost to perform that movement (Wang & Dounskaia, 2012; Goble et al., 2007).

For inertial contributions and BBC moments to *assist* joint motion, the neural output to a muscle opposing these *assistive* moments should be reduced, or even inhibited. Such a scenario would allow inertia and the BBC moments to *assist* in rotating the joint, without being counteracted by opposing muscle activation (e.g., a flexor motion being opposed by a muscle causing an extensor moment). Surround inhibition (SI) is a physiological mechanism that may facilitate the use of inertia and BBC moments to *assist* joint motion, specifically by inhibiting neural output to muscles that oppose that joint motion. SI is strongest (i.e., greatest inhibition) in muscles that are in close proximity to the active muscle and increases in strength as the onset of movement approaches (Sohn & Hallett, 2004; Beck & Hallett, 2011). Reduced SI is thought to contribute to motor impairments in clinical populations (Beck, Schubert, Richardson, & Hallett, 2009; Beck et al., 2008; Shin, Kang, & Sohn, 2007). It is not known whether SI exists in muscles performing

multi-joint movements, but, if so, SI may allow inertia and BBC moments to *assist* joint motion by reducing neural output to muscles creating moments in the opposite direction.

In the present study, goal-directed arm movements were used to investigate corticospinal output in two mono-articular shoulder (pectoralis major, posterior deltoid) and two bi-articular shoulder-elbow (biceps brachii, triceps brachii) muscles. The purpose of the present study was to investigate: 1) how using inertia and BBC moments to contribute to joint motion influences corticospinal output to muscles of the arm and 2) surround inhibition in arm muscles involved in multi-joint movements. This is the first investigation of inertial influences and BBC moments on corticospinal output during different movement phases (i.e., pre-movement, muscle activity onset and during movement) and when reaching to a variety of spatial targets that require a unique combination of net muscle moments and BBC moments at the shoulder and elbow joints. This is also the first investigation of SI in multi-joint upper arm movements.

4.3 Methods

4.3.1 Participants

Fifteen (Mean = 23.2, SD = 5.6, 8 females) adults participated. All participants were right handed as determined using a modified version of the Edinburgh Handedness Inventory (Oldfield, 1971) and were screened for any contra-indicators of TMS (i.e., no intake of benzodiazepines). Written informed consent was obtained from all individuals prior to participation in the study. This research was approved by the McMaster Research Ethics Board in accordance to the Declaration of Helsinki.

4.3.2 Electromyography

Surface Ag/AgCl electromyography (EMG) electrodes were placed on muscles of the right arm that included; biceps brachii long head (BB), triceps brachii long head (TB), pectoralis major (PM), posterior deltoid (PD). For all muscles, two electrodes were placed on the muscle belly with an inter-electrode distance of ~ 3 cm. This bipolar montage was used to quantify muscle activity and corticospinal excitability throughout the behavioural task. For the BB and TB, there was also an extra electrode placed on the lateral epicondyle to allow for a monopolar recording from these muscles. This monopolar set-up was only necessary for determining resting motor threshold (RMT). The ground electrode was placed on the medial epicondyle. The right arm performed the task while the left arm remained relaxed throughout the experiment. EMG was amplified (x 1000), band-pass filtered (20 and 2500 Hz) (Intronix Technologies Corporation Model

2024F, Bolton, Canada) and sampled at a frequency of 10 KHz using an analog-to-digital interface system (Power 1401, Cambridge Electronic Design, Cambridge, UK).

4.3.3 Transcranial Magnetic Stimulation

Monophasic single TMS pulses were delivered using two custom built 50 mm diameter figure-of-eight branding coils connected to two Magstim 200^2 stimulators (Magstim, Whitland, UK). Coil position and orientation were monitored using optical sensors placed on the coil and the participant (Brainsight Neuronavigation, Rogue Research, Montreal, Canada). The motor hot spot for BB was determined first by orienting the coil at 45° in relation to the parasagittal plane to induce a posterior-lateral to anterior-medial current in the cortex and preferentially activate corticospinal neurons trans-synaptically (Rothwell et al., 1999). The position of the coil and intensity of the stimulator were adjusted until the optimal hot spot for BB was found, which was defined as the lowest stimulator intensity to evoke MEPs of ~500 μV in BB. The second coil was used to determine the motor hot spot for the TB using the aforementioned method. Resting motor threshold (RMT) was determined for both BB and TB at their motor hotspots and defined as the minimum stimulator intensity to evoke a 50 μV response in the targeted muscle in 5 out of 10 consecutive trials. The BB hotspot was used to evoke MEPs in BB and PM. The TB hotspot was used to evoke MEPs in TB and PD. The TMS stimulator was set to 1.2 RMT for each hotspot and held constant throughout the experiment.

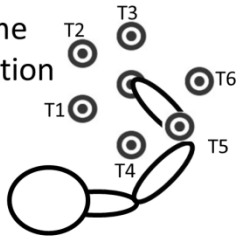
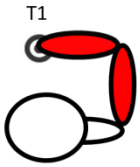
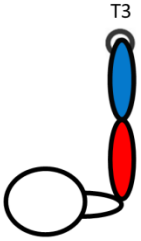
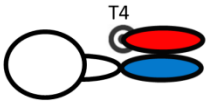
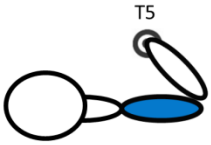
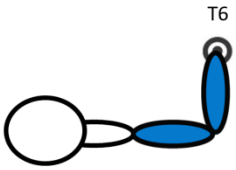
4.3.4 Behavioural Task

Participants performed a reaching task to targets located in peripersonal space. Movements were restricted to the transverse (horizontal) plane by having the right arm fastened in a custom made exoskeleton (80/20 Inc., Columbus City, USA) to minimize friction and eliminate the contribution of gravity to joint moments during movement. Polhemus FASTRAK was used to monitor arm posture by placing sensors on bony landmarks to represent the trunk orientation (suprasternal notch) and joint locations of arm segments including, the right acromion process (shoulder), the right lateral epicondyle (elbow), and between the radial and ulnar styloid processes (wrist) (Nussbaum & Zhang, 2000).

The initial position of the arm is shown in *Figure 4.1A (top left)* whereby the shoulder was abducted to 90° and at 45° flexion in relation to the frontal plane and the elbow was positioned at 90° flexion in relation to the upper arm. This arm posture defined the 'home' position for the task. Movements to each target started from the home position. Participants were instructed to perform movements as quickly and accurately as possible to one of the six different targets depicted in *Figure 4.1A*. The approximate end arm postures for each target are also presented in *Figure 4.1A*. Target $S_F E_F$ (T1) required participants to actively flex their shoulder 45° and actively flex their elbow 45°. To complete this movement, a net flexor moment was required at the shoulder and elbow joint and the inertia of the segments and BBC moments would *resist* flexion at both joints. Target $S_F E_0$ (T2) required participants to actively flex their shoulder 45° and

passively extend the elbow, thereby requiring a net flexor moment at the shoulder and no net moment at the elbow. The inertia of the forearm, hand, and apparatus, and to a lesser extent the BBC moment, would *assist* elbow joint extension. Target $S_F E_E$ (T3) required participants to actively flex their shoulder 45° and actively extend their elbow 45°, thereby requiring a net flexor moment at the shoulder and net extensor moment at the elbow. The inertia of the segment would have to be overcome to reach the target, but the BBC moment would *assist* shoulder flexion and elbow extension. Target $S_E E_F$ (T4) required participants to actively extend their shoulder 45° and actively flex their elbow 45° thereby requiring a net extensor shoulder moment and a net flexor elbow moment. The inertia of the segment would have to be overcome to reach the target, but the BBC moments would *assist* shoulder extension and elbow flexion. Target $S_E E_0$ (T5) required participants to actively extend their shoulder 45° and passively flex the elbow joint thereby requiring a net flexor shoulder moment and no net moment at the elbow. The inertia of the forearm, hand, and apparatus, and to a lesser extent the BBC moment, would *assist* elbow joint flexion. Target $S_E E_E$ (T6) required participants to actively extend their shoulder 45° and actively extend their elbow 45° thereby requiring a net extensor moment at both the shoulder and elbow. The inertia of the segments and BBC moments would *resist* both joints' extensor rotations. The home position and each of the six targets were adjusted to each participant's segment lengths and the movement amplitude was the same for each target within a participant.

A

Home Position 		Net Elbow Moment		
		Flexor (E_F)	No Moment (E_0)	Extensor (E_E)
Net Shoulder Moment	Flexor (S_F)	No elbow angle change  **S_FE_F**	Elbow Extension  **S_FE_0**	Elbow Extension +  **S_FE_E**
	Extensor (S_E)	Elbow Flexion +  **S_EE_F**	Elbow Flexion  **S_EE_0**	No elbow angle change  **S_EE_E**

B

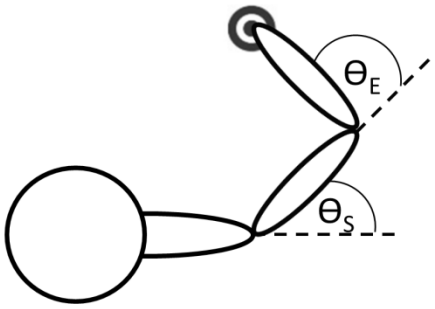


Figure 4.1. Six targets that participants were required to reach towards from the home position. A: At the home target, the shoulder was abducted at 90° and flexed 45° in the transverse (horizontal) plane, while the elbow was flexed 90° in relation to the upper arm (i.e., home position). The different arm configurations and net moments to reach the 6 target are described in the 6 cells. A red segment requires a net flexor moment to reach the target. A blue segment requires a net extensor moment to reach the target. The columns and rows describe the directions of the net elbow and shoulder moments, respectively, required to successfully reach to the target. The six targets are defined based on the net moment required at each joint. Target S_FE_F: shoulder flexor moment, elbow flexor moment; Target S_FE_0: shoulder flexor moment, no net elbow moment; Target S_FE_E: shoulder flexor moment, elbow extensor moment; Target S_EE_F: shoulder extensor moment, elbow flexor moment; Target S_EE_0: shoulder extensor moment, no net elbow moment; Target S_EE_E: shoulder extensor moment, elbow extensor moment. **B**: The arm posture at the home position. Θ_S defines the shoulder angle, while Θ_E defines the elbow angle.

Participants viewed a computer monitor that displayed the target location and a crosshair cursor controlled by the wrist FASTRAK sensor to indicate the instantaneous location of the limb endpoint. Each trial began with the cursor at the home position. A visual target (one of 6 possible targets, *Figure 4.1A*) appeared followed 2 – 3 s later by an auditory 'go' cue that signalled participants to begin their movement. The location of the visual target presented was randomized across trials. The trial ended when the participant placed the cursor in the target position and remained in this position for 1 s. If the target location was held for a duration shorter than 1 s, or the target was not acquired within 3 s of the 'go' cue, the trial was deemed a 'missed target' trial and excluded from further analysis. At the end of the trial, the home position visual target appeared and participants returned to this position. This 'home' position could only be achieved by one combination of shoulder and elbow angle. TMS was triggered at three phases following the 'go' cue (*Figure 4.2*); 1) Pre-movement phase (PMP) delivered TMS 100 ms after the

'go' cue, 2) EMG onset phase (EOP) delivered TMS when EMG in BB or TB exceeded 100 μV in either muscle, whichever muscle reached the threshold first, 3) Movement phase (MP) delivered TMS when the shoulder angle (from an electrogoniometer) increased by 15 ° in flexion or extension from the home position. A custom made sequencer file (Signal software, version 6.01, Cambridge Electronic Design, Cambridge, UK) triggered the TMS pulse for the EOP and MP phases. Additionally, a 'no movement' trial was included whereby a target was not presented and participants did not respond to the subsequent 'go' cue. In these 'no-movement' trials, TMS was delivered at 100 ms, 200 ms, or 500 ms after the 'go' cue to mimic the timing of the TMS pulses delivered in the three phases (PMP, EOP and MP), respectively. In total, 21 trial types were delivered (6 targets & 1 'no movement') x 3 phases (PMP, EOP, MP). Each trial type was repeated 10 times throughout the experiment (i.e., 210 trials) –one set for the BB hotspot and one set for the TB hotspot (i.e., 2 x 210 = 420 trials in total). Within each block, testing was performed on a single motor hotspot (i.e., either BB or TB hotspot). Further, 21 different trial types were randomly presented within the block of trials. Twenty blocks of trials were performed in total. Additionally for each trial type, we predicted which muscles would, and would not, be primarily involved in the task. When a muscle was predicted to not be involved in the task, it was expected that surround inhibition would reduce activity to this muscle. Targets that tested surround inhibition for a muscle are highlighted in Table 4.1.

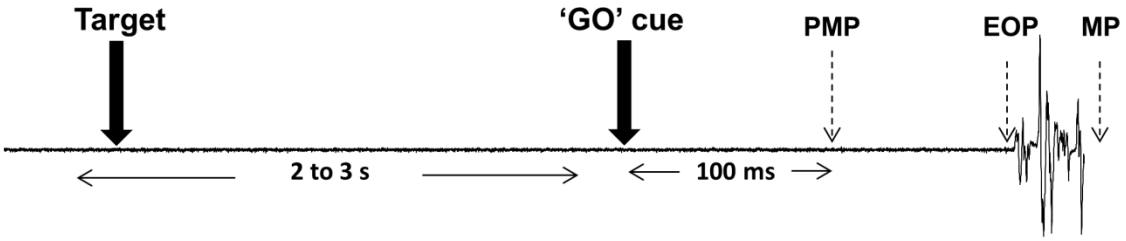


Figure 4.2. Timeline of each trial performed in the behavioural task. A visual cue was displayed to the participant, followed 2-3 s later by an auditory 'go' cue to begin the movement. Three different TMS triggers are depicted in the timeline; Pre-movement phase (PMP) where the TMS was triggered 100 ms after the 'go' cue; EMG onset phase (EOP) where the TMS was trigger once EMG crossed 100 μV threshold in either BB or TB; Movement phase (MP) where TMS was triggered once the shoulder angle reached either 15° of flexion or extension from the home target.

Table 4.1. Muscles that surround inhibition was tested on. The left column indicates the target that the participant was going to reach towards. The right column indicates the muscles surround inhibition was predicted to occur for that specific target in the corresponding row.

Target	Surround Inhibition Muscle(s)
T1: S_FE_F	PD, TB
T2: S_FE_0	PD
T3: S_FE_E	BB, PD
T4: S_EE_F	PM, TB
T5: S_EE_0	PM
T6: S_EE_E	BB, PM

4.3.5 Data Analysis

MEPs

The peak-to-peak amplitude of the MEP was obtained from 4 different muscles (BB, TB, PM, PD). Each amplitude was normalized to a 'no-movement' condition for one of the

analyses. Specifically, MEPs from the PMP, EOP, and MP were normalized to the time-locked 'no-movement' conditions, whereby TMS was delivered either at 100 ms, 200 ms, and 500 ms after the 'go' cue, respectively.

Kinematics and Kinetics

Kinematic measures were computed based on the filtered marker coordinate data and arm segment model. The marker coordinate data were sampled at 30 Hz and filtered using a dual pass second order Butterworth filter with a cut-off frequency of 6 Hz, as determined from a residual analysis (Winter, 2009). Relative joint angles were calculated for the shoulder and elbow joints. The shoulder angle was determined from the trunk, shoulder, and elbow sensor, while the elbow angle was determined from the shoulder, elbow, and wrist sensor. The wrist angle was not calculated because the wrist joint was fixed with the wrist splint. The shoulder and elbow angle definitions are shown in *Figure 4.1B*. The first and second derivative of the angular displacement data were used to determine angular velocity and angular acceleration, respectively, of the shoulder and elbow angle.

Joint kinetics were calculated using the kinematic data of the participant and the mass, length, and inertial characteristics of the participant's arm and the custom made exoskeleton (Winter, 2009). See Appendix 1 for the anthropometric calculations. Using this information, bone on bone contact (BBC) moments, net moments, and estimated muscle moments were calculated. The overall net moments and BBC moments are determined based on the inertial properties of the segments and accelerations of the

shoulder and elbow joints. The residual moment was calculated and defined as the predicted muscle moment. The equations used for the moment analysis are presented in Appendix 2.

4.4 Statistical Analysis

4.4.1 Pre-Movement Phase

To investigate if the modulation of corticospinal output to muscles of the arm was influenced by the upcoming movement to target locations with varying inertial and BBC moment contributions to joint rotations, a repeated measures ANOVA with factor TARGET (6 levels; targets 1-6) was completed independently for each muscle (BB, TB, PM, PD) using the dependent measure of normalized MEP amplitude ($MEP_{Normalized} = \frac{MEP_{movement}}{MEP_{no\ movement}}$). This normalization allowed for determining relative increases or decreases in corticospinal excitability in relation to a condition when the participant was not performing the task. If a significant main effect was found, a post hoc Tukey's HSD was used to locate the differences between the means. Alpha value was set at $p < 0.05$ for each repeated measures ANOVA.

To investigate surround inhibition in arm muscles involved in multi-joint movements during PMP, planned comparisons were used between the MEP from the 'no-movement' condition and the MEP during the PMP for certain muscles. A modified Bonferroni test was completed on the 'no movement' condition and each target that a muscle was

predicted to not be involved in the task (Keppel, 1991). Table 4.1 presents the targets that the muscle was predicted to be inhibited.

4.4.2 EMG Onset Phase

To investigate if EOP corticospinal output to muscles of the arm was influenced by the upcoming movement to target locations with varying inertial and BBC moment contributions to joint rotations, a repeated measures ANOVA with factor TARGET (6 levels; targets 1-6) was completed independently for each muscle (BB, TB, PM, PD) using the dependent measure of normalized MEP amplitude ($MEP_{Normalized} = \frac{MEP_{movement}}{MEP_{no\ movement}}$). If a significant main effect was found, a post hoc Tukey's HSD was used to locate the differences between the means. Alpha value was set at $p < 0.05$ for each repeated measures ANOVA.

To investigate surround inhibition in arm muscles involved in multi-joint movements during EOP, planned comparisons were used between the MEP from the 'no-movement' condition and the MEP during the EOP for certain muscles. A modified Bonferroni test was completed on the 'no-movement' condition and each target that a muscle was predicted to not be involved in the task (Keppel, 1991). Table 4.1 presents the targets that the muscle was predicted to be inhibited.

4.4.3 Movement Phase

To investigate if MP corticospinal output to muscles of the arm was influenced by the movement to target locations with varying inertial and BBC moment contributions to joint rotations, a repeated measures ANOVA with factor TARGET (6 levels; targets 1-6) was completed independently for each muscle (BB, TB, PM, PD) using the dependent measure of normalized MEP amplitude ($MEP_{Normalized} = \frac{MEP_{movement}}{MEP_{no\ movement}}$). If a significant main effect was found, a post hoc Tukey's HSD was used to locate the differences between the means. Alpha value was set at $p < 0.05$ for each repeated measures ANOVA.

4.5 Results

Participants reached toward six different targets. Of the 420 trials each participant completed, on average, they only missed a low number of trials($\bar{X} = 9.07, SD = 7.35$). The mean reaction time in seconds was ($\bar{X} = 0.229, SD = 0.059$) for target 1, ($\bar{X} = 0.271, SD = 0.059$) for target 2, ($\bar{X} = 0.206, SD = 0.034$) for target 3, ($\bar{X} = 0.222, SD = 0.040$) for target 4, ($\bar{X} = 0.232, SD = 0.041$) for target 5, and ($\bar{X} = 0.243, SD = 0.047$) for target 6.

The mean movement time in seconds was ($\bar{X} = 0.926, SD = 0.178$) for target 1, ($\bar{X} = 0.896, SD = 0.140$) for target 2, ($\bar{X} = 0.875, SD = 0.144$) for target 3, ($\bar{X} =$

$0.836, SD = 0.155$) for target 4, ($\bar{X} = 0.896, SD = 0.168$) for target 5, and ($\bar{X} = 0.910, SD = 0.162$) for target 6.

4.5.1 Pre-Movement Phase

The means of the MEP values for each muscle toward each target in the PMP is displayed in *Figure 4.3* and results from the ANOVA are presented in Table 4.2. In the PMP, there was a significant main effect of TARGET for BB, PM, PD, but not TB. For BB, the MEPs were significantly larger at $S_F E_F$ (in relation to all targets, except T4), suggesting that corticospinal output is greater when the anticipated inertial contribution and BBC moments *resist* the intended flexion rotation at both the shoulder and elbow joints. Although we expected that similar results would be found for the bi-articular TB muscle such that corticospinal output would be the largest when the inertial contribution and BBC moments *resist* the extension rotation at both joints, the ANOVA did not reveal this result. The MEP was larger in PM and PD when reaching towards targets requiring shoulder flexion and shoulder extension, respectively (i.e., *Figure 4.3*, see PM targets 1, 2 and 3 and PD targets 4, 5 and 6). Further, PD corticospinal output was significantly larger when the anticipated movement was toward $S_E E_E$, suggesting that, for this mono-articular shoulder extensor muscle, the corticospinal output was greater when the inertial effect and BBC moments *resist* the shoulder extension. Muscles that are predicted to participate in surround inhibition are shown in Table 4.1 and the corresponding mean MEPs (with standard error) are shown in *Figure 4.4*. Surround inhibition was only

present in the PD when the participant was reaching towards $S_F E_E$ (Target 3) ($t_{(14)}$ = 2.676, p = 0.018, d = 0.14).

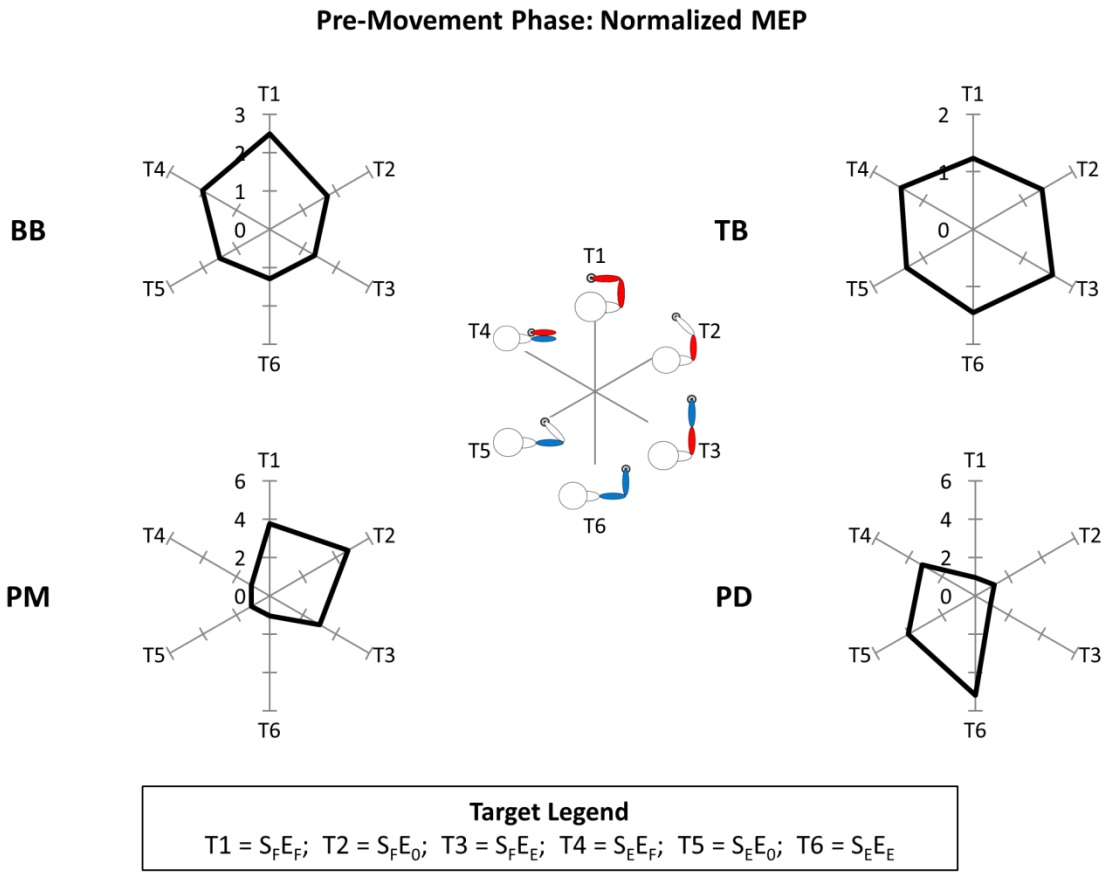


Figure 4.3. Normalized MEP amplitude of the upper arm muscles during the Pre-Movement Phase when reaching to the six different targets (T1-T6). The polar plots depict the group mean values of the normalized MEP recorded from BB, TB, PM, and PD.

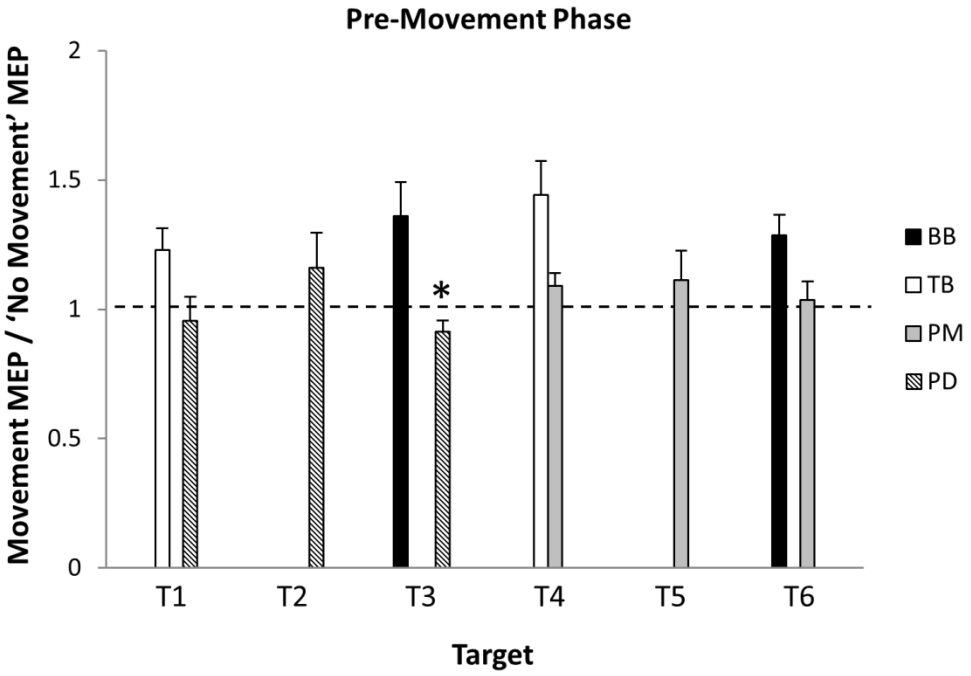


Figure 4.4. Surround inhibition recorded during the PMP in the upper arm muscles. The ordinate is the normalized MEP amplitude (i.e., movement MEP/'no-movement' MEP) and the abscissa is the target that the participant was signalled to reach towards. If a bar is not present for a target location, it indicates that surround inhibition was not tested for that muscle when reaching to that target. An asterisk indicates target locations for which the MEP was significantly reduced in the 'movement' trial in relation to the 'no-movement' trial.

Table 4.2. ANOVA results for the effect of TARGET on MEP for each upper arm muscle monitored. MEP muscle indicates the muscle the MEP was recorded from and used in the ANOVA and the phase the MEP was recorded in is in the same row. *df* = degrees of freedom, *F* = F-statistic, *p* = *p*-value, ω^2 = effect size calculated with omega-square.

Phase	MEP Muscle	*df*	*F*	*p*	ω^2	Tukey's HSD Post-hoc
PMP	Biceps Brachii	5, 70	4.951	0.020	0.20	T1 > T2 & T3 & T5 & T6
	Triceps Brachii	5, 70	1.498	0.238	0.21	N/A
	Pectoralis Major	5, 70	5.256	0.025	0.21	T1 > T4 & T5 & T6; T2 > T4 & T5 & T6
	Posterior Deltoid	5, 70	12.345	<0.0001	0.42	T1 < T4 & T5 & T6; T2 < T4 & T5 & T6; T3 < T4 & T5 & T6; T4 < T6
EOP	Biceps Brachii	5, 70	22.855	<0.0001	0.59	T1 > T2 & T3 & T5 & T6; T2 < T5 & T4; T3 < T5 & T4; T4 > T5 & T6
	Triceps Brachii	5, 70	0.721	0.461	0	N/A
	Pectoralis Major	5, 70	9.497	<0.0001	0.36	T1 > T4 & T5 & T6; T2 > T4 & T5 & T6; T3 > T4 & T5 & T6
	Posterior Deltoid	5, 70	12.890	<0.0001	0.43	T1 v. T4 & T5 & T6; T2 v. T4 & T5 & T6; T3 v. T4 & T5 & T6
MP	Biceps Brachii	5, 70	15.443	<0.0001	0.48	T1 > T3 T1 < T4, T5; T2 < T4, T5, T6; T3 < T4, T5, T6
	Triceps Brachii	5, 70	1.696	0.209	0.04	N/A
	Pectoralis Major	5, 70	.505	0.566	0	N/A
	Posterior Deltoid	5, 70	2.260	0.148	0.07	N/A

Target Legend

T1 = S_FE_F; T2 = S_FE_0; T3 = S_FE_E; T4 = S_EE_F; T5 = S_EE_0; T6 = S_EE_E

4.5.2 EMG Onset Phase

The mean MEPs for each muscle toward each target in the EOP, are displayed in *Figure 4.5* and ANOVA results are presented in Table 4.2. Results from the EOP were very similar to the PMP. BB MEPs were significantly larger at S_FE_F, further suggesting the influence *resistive* inertial effects and BBC moments have on corticospinal output prior to movement. Corticospinal output to TB was not significantly affected by target location and MEPs were larger from PM and PD when reaching towards targets requiring shoulder flexion and shoulder extension, respectively (i.e., *Figure 4.5*, see PM targets 1, 2 and 3 and PD targets 4, 5 and 6). One notable difference between PMP and EOP was that, although the PD MEPs were larger prior to reaching to S_EE_E, they were not significantly different for the other shoulder extension targets (i.e., S_EE_0, S_EE_F). The results of the surround inhibition analysis tested during EOP are presented in *Figure 4.6*. Similar to the PMP, surround inhibition was not present in any muscle while preparing to reach any target location.

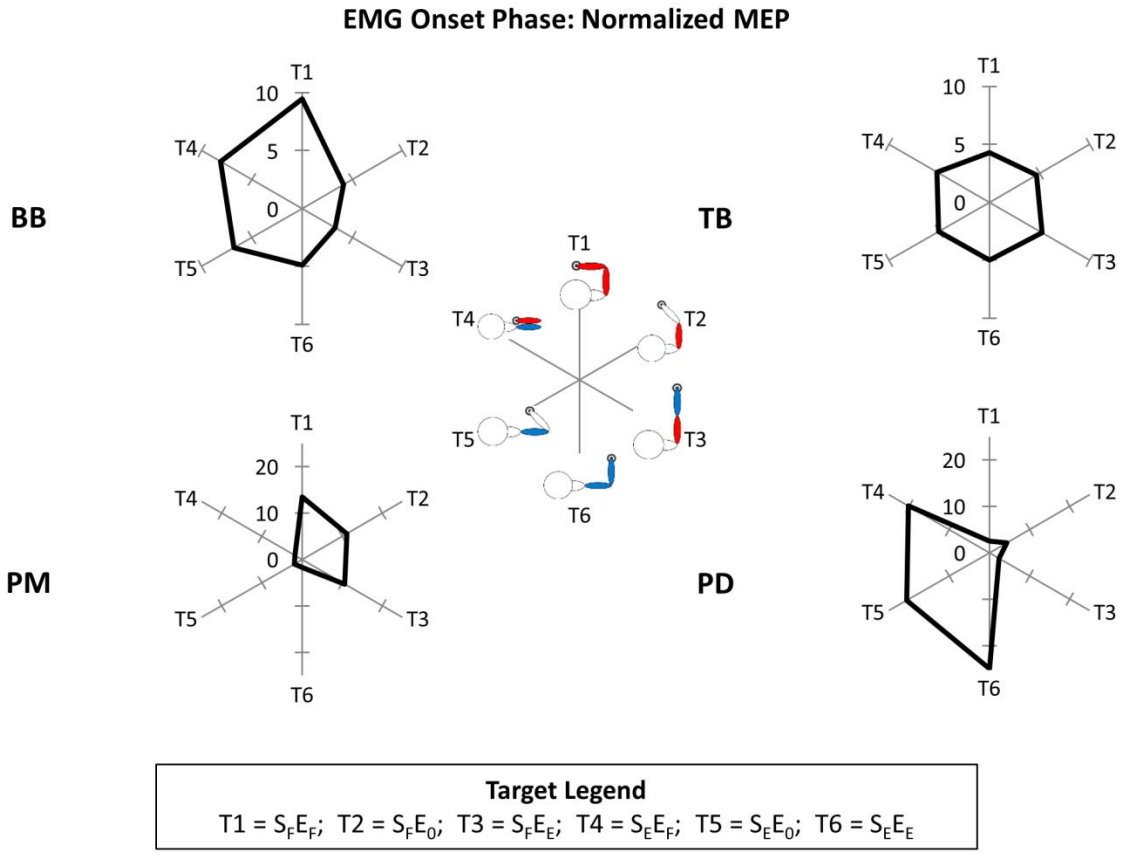


Figure 4.5. Normalized MEP amplitude of the upper arm muscles during the EOP when reaching to the six different targets (T1-T6). The polar plots depict the group mean values of the normalized MEP recorded from BB, TB, PM, and PD.

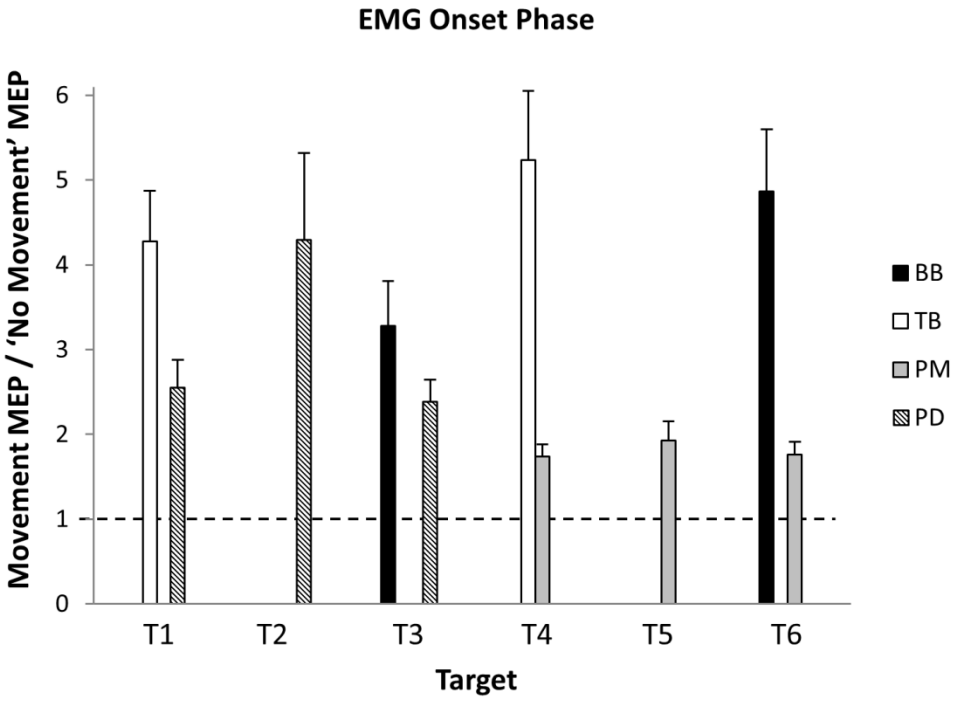


Figure 4.6. Surround inhibition recorded during the EOP in the upper arm muscles. The ordinate is the normalized MEP amplitude (i.e., movement MEP/'no-movement' MEP) and the abscissa is the target that the participant was signalled to reach towards. If a bar is not present for a target location, it indicates that surround inhibition was not tested for that muscle when reaching to that target. An asterisk indicates target locations that the MEP was significantly reduced in the 'movement' trial in relation to the 'no-movement' trial.

4.5.3 Movement Phase

The mean MEPs for each muscle toward each target in the MP are displayed in *Figure 4.7* and ANOVA results are in Table 4.2. Unlike the PMP and EOP, there was no significant effect of target location on the MEPs for all muscles (i.e., relatively low effect size and non-significant main effects) except for BB. For BB, the MEPs were modulated by target location; however, the trends were different with MEPs being larger during shoulder extension targets. The group-averaged data led to a further analysis that

explored the actual movement profiles for individual participants to address whether the BBC moments were in fact *assistive* or *resistive* of the joint motion when the MEP was elicited, as we originally anticipated.

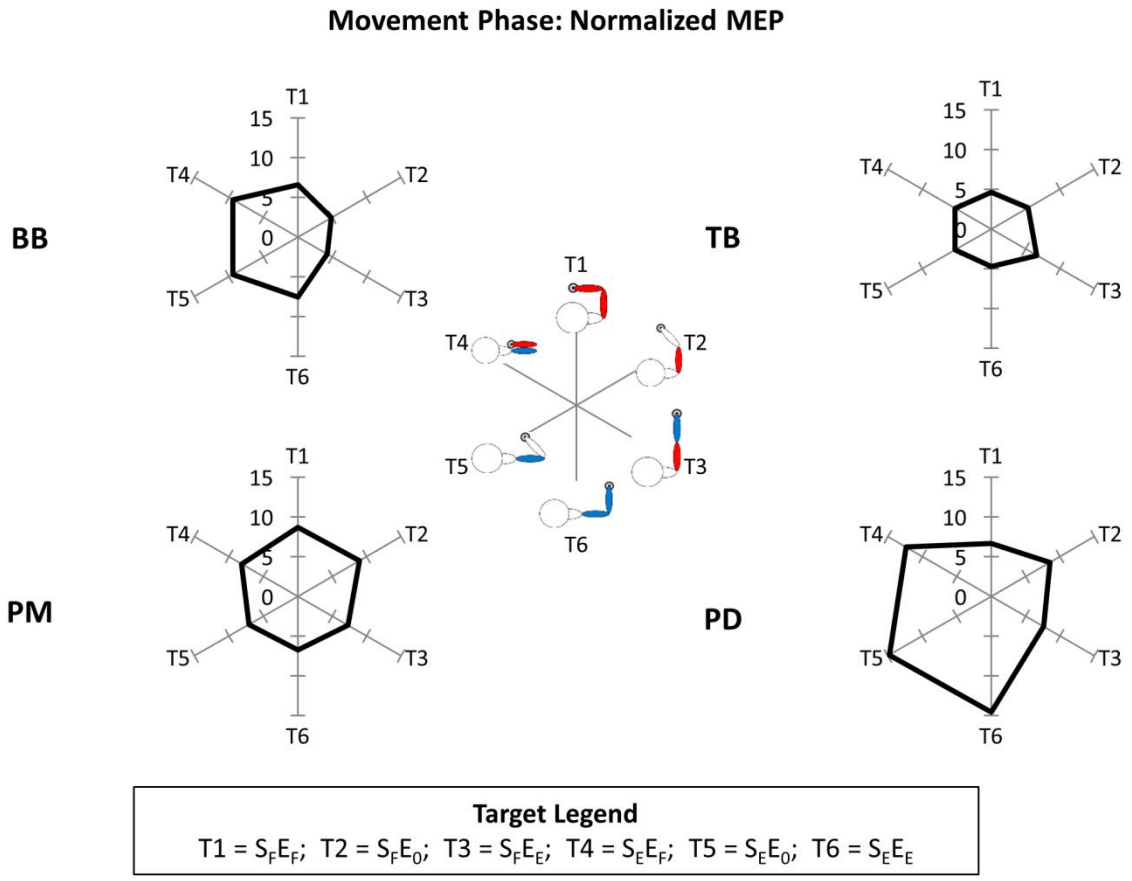


Figure 4.7. Normalized MEP amplitude of the upper arm muscles during the MP when reaching to the six different targets (T1-T6). The polar plots depict the group mean values of the normalized MEP recorded from BB, TB, PM, and PD.

Specifically, during MP we expected certain combinations of *resistive* and *assistive* BBC moments depending on the target location (e.g., the BBC moment would *resist* the shoulder and elbow net flexor moment, and rotation, when reaching to target S_FE_F).

Analysis of the individual profiles, however, revealed that the expected combinations of BBC at the shoulder and elbow joints did not occur for all participants (see *Figure 4.8* and 4.*9* for shoulder and elbow moments, respectively*)*. As can be seen, there were many points in time where the BBC moment was in a different direction than what was expected. Therefore, based on the variability of moment profiles across individuals, we investigated the relationship between MEP amplitude and BBC moments by removing the latter from target space and re-assigning them as *resistive* or *assistive* based on their direction relative to the net moment direction. BBC moments were assigned *assistive* if they occurred in the same direction as the net moment and *resistive* if they occurred in the direction opposite to the net moment. If the BBC moment was in the opposite direction of the net moment, it was given a negative sign. See *Figure 4.8* (Target 1 – middle column, top row), for a profile that the BBC moment was *resistive* at the shoulder joint. If the BBC moment was in the same direction of the net moment, it was given a positive sign. See *Figure 4.8* (Target 4 – middle column, 4th row), for a profile that the BBC moment was *assistive* at the shoulder joint.

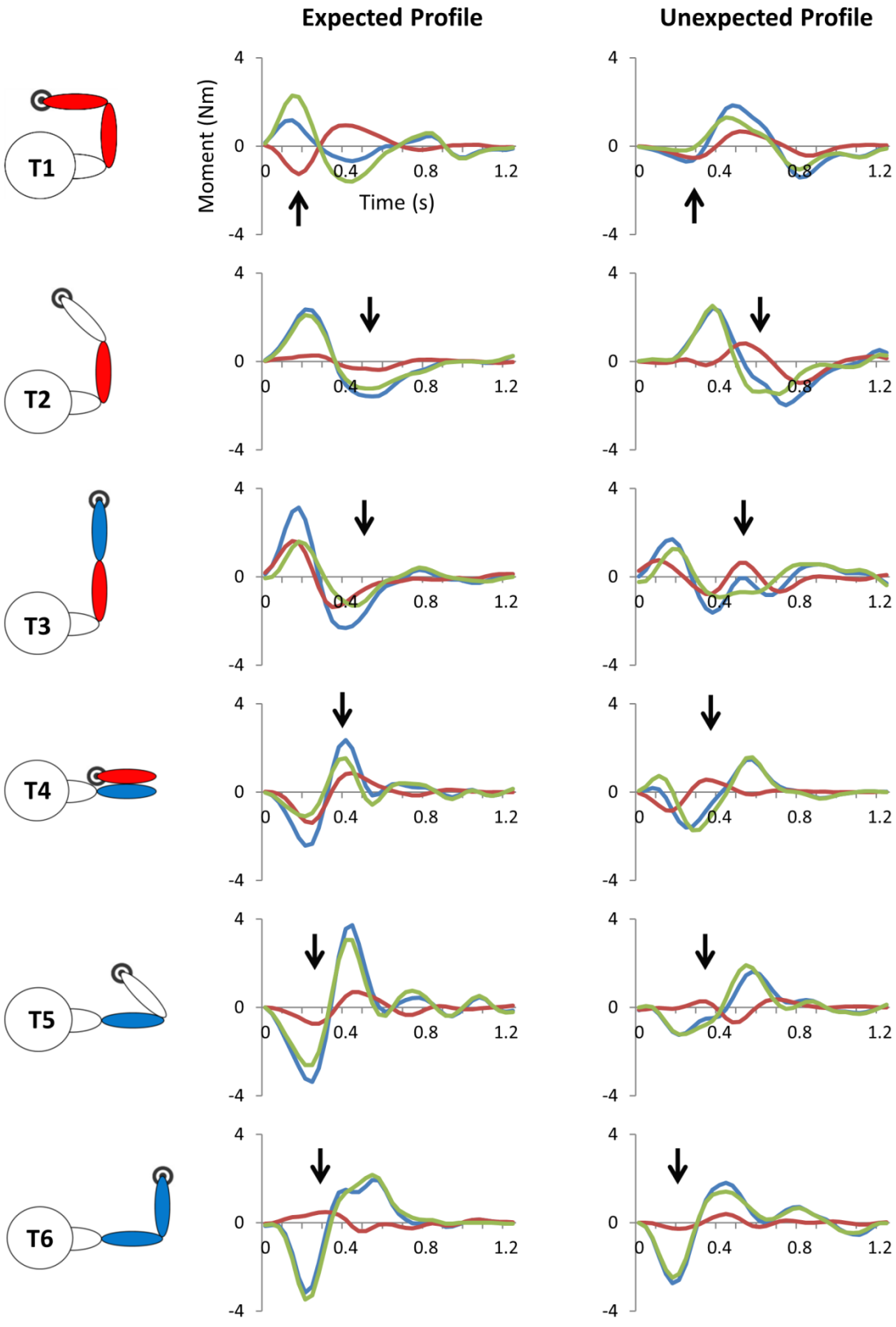

Expected Profile
Unexpected Profile
Moment (Nm)
Time (s)
T1
T2
T3
T4
T5
T6
4
0
-4
0
0.4
0.8
1.2

Figure 4.8. Representative shoulder moment-time profiles of two different participants reaching to the six different targets. Positive and negative values indicate a flexor and extensor moment, respectively. The blue, red, and green lines depict the net, bone on bone contact (BBC), and muscle moments about the joint. The left column displays the target locations that correspond to the moment-time profiles in the same row. The middle column displays the representative profiles from one subject that produced the expected moment-time profiles based on the target location. The right column displays the representative profiles from one subject that produced different or unexpected moment-time profiles based on the target location. Target 1: it was expected that the BBC moment would *resist* (i.e., oppose) the net moment at the shoulder as seen in the expected profile, but some participants performed a movement such that the BBC moment *assisted* the shoulder net moment as seen in the unexpected profile. Target 2: it was expected that the BBC moment would *assist* the net moment at the shoulder as seen in the expected profile, but some participants performed a movement such that the BBC moment *resisted* (i.e., opposed) the shoulder net moment as seen in the unexpected profile. Target 3: it was expected that the BBC moment would *assist* the net moment at the shoulder as seen in the expected profile, but some participants performed a movement such that the BBC moment *resisted* (i.e., opposed) the shoulder net moment as seen in the unexpected profile. Target 4: it was expected that the BBC moment would *assist* the net moment at the shoulder as seen in the expected profile, but some participants performed a movement such that the BBC moment *resisted* (i.e., opposed) the shoulder net moment as seen in the unexpected profile. Target 5: it was expected that the BBC moment would *assist* the net moment at the shoulder as seen in the expected profile, but some participants performed a movement such that the BBC moment *resisted* (i.e., opposed) the shoulder net moment as seen in the unexpected profile. Target 6: it was expected that the BBC moment would *resist* (i.e., oppose) the net moment at the shoulder as seen in the expected profile, but some participants performed a movement such that the BBC moment *assisted* the shoulder net moment as seen in the unexpected profile.

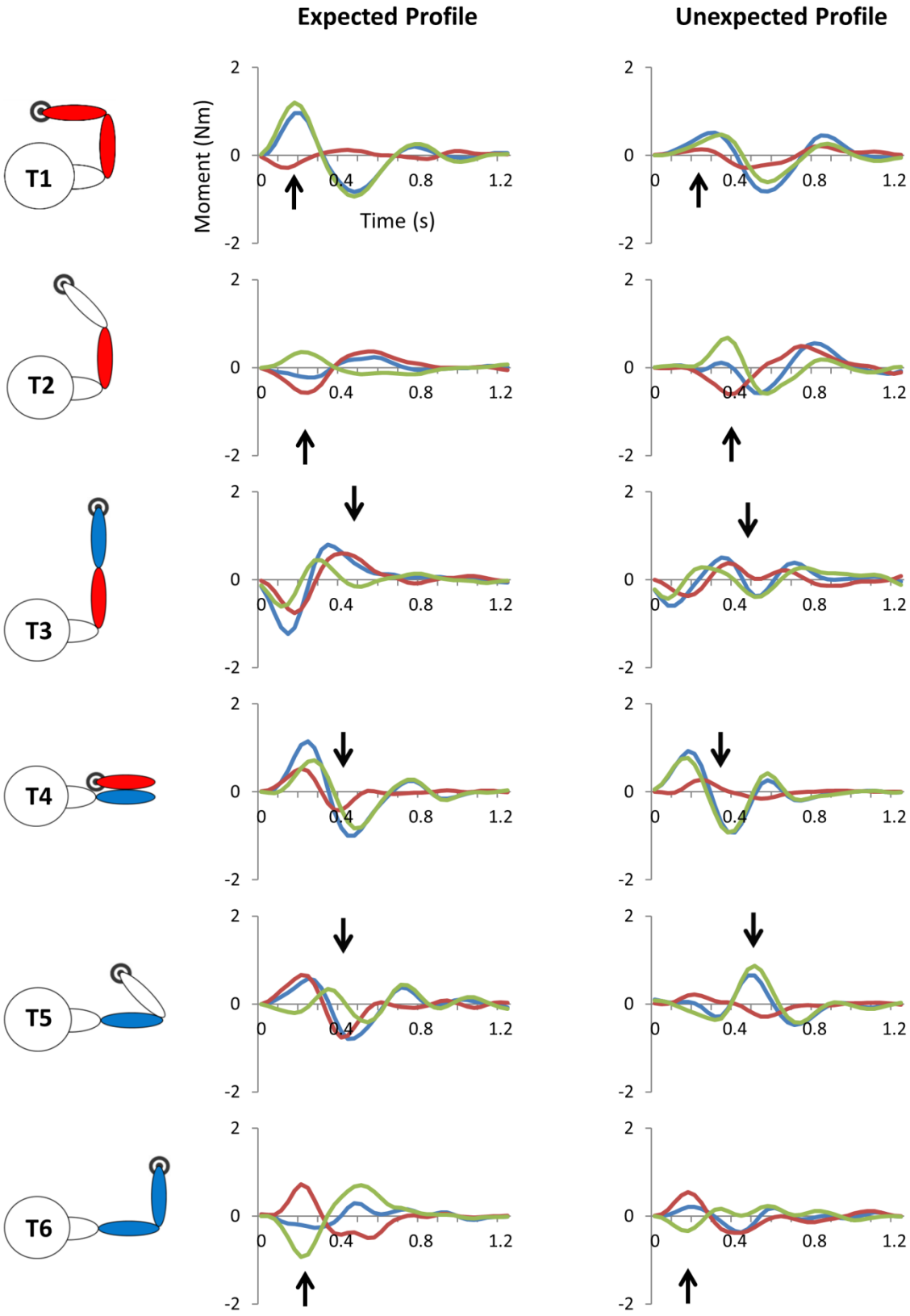

Expected Profile
Unexpected Profile
Moment (Nm)
Time (s)
T1
T2
T3
T4
T5
T6
2
0
-2
0
0.4
0.8
1.2

Figure 4.9. Representative elbow moment-time profiles of two different participants reaching to the six different targets. Positive and negative values indicate a flexor and extensor moment, respectively. The blue, red, and green lines depict the net, bone on bone contact (BBC), and muscle moments at the joint. The left column shows the target locations that correspond to the moment-time profiles in the same row. The middle column displays the representative profiles from one subject that produced the expected moment-time profiles based on the target location. The right column displays the representative profiles from one subject that produced different or unexpected moment-time profiles based on the target location. Target 1: it was expected that the BBC moment would *resist* (i.e., oppose) the net moment at the elbow as seen in the expected profile, but some participants performed a movement such that the BBC moment *assisted* the elbow net moment as seen in the unexpected profile. Target 2: it was expected that the BBC moment would *assist* the net moment at the elbow as seen in the expected profile, but some participants performed a movement such that the BBC moment *resisted* (i.e., opposed) the elbow net moment as seen in the unexpected profile. Target 3: it was expected that the BBC moment would *assist* the net moment at the elbow as seen in the expected profile, but some participants performed a movement such that the BBC moment *resisted* (i.e., opposed) the elbow net moment as seen in the unexpected profile. Target 4: it was expected that the BBC moment would *assist* the net moment at the elbow as seen in the expected profile, but some participants performed a movement such that the BBC moment *resisted* (i.e., opposed) the elbow net moment as seen in the unexpected profile. Target 5: it was expected that the BBC moment would *assist* the net moment at the elbow as seen in the expected profile, but some participants performed a movement such that the BBC moment *resisted* (i.e., opposed) the elbow net moment as seen in the unexpected profile. Target 6: it was expected that the BBC moment would *resist* (i.e., oppose) the net moment at the elbow as seen in the expected profile, but some participants performed a movement such that the BBC moment *assisted* the elbow net moment as seen in the unexpected profile.

Following the assignment of BBC moments, Pearson's product moment correlation coefficient was calculated between individual MEPs of each upper arm muscles and their corresponding *resistive* and *assistive* BBC moments. *Figure 4.10* displays the group-averaged means of the MEP and BBC moments for each correlation analysis performed and Table 4.3 displays the statistical results of the correlational analysis. The correlational analysis revealed that there was an inverse relationship between

corticospinal output of all muscles and the magnitude of BBC moments when they *resisted* the net moment at the shoulder joint.

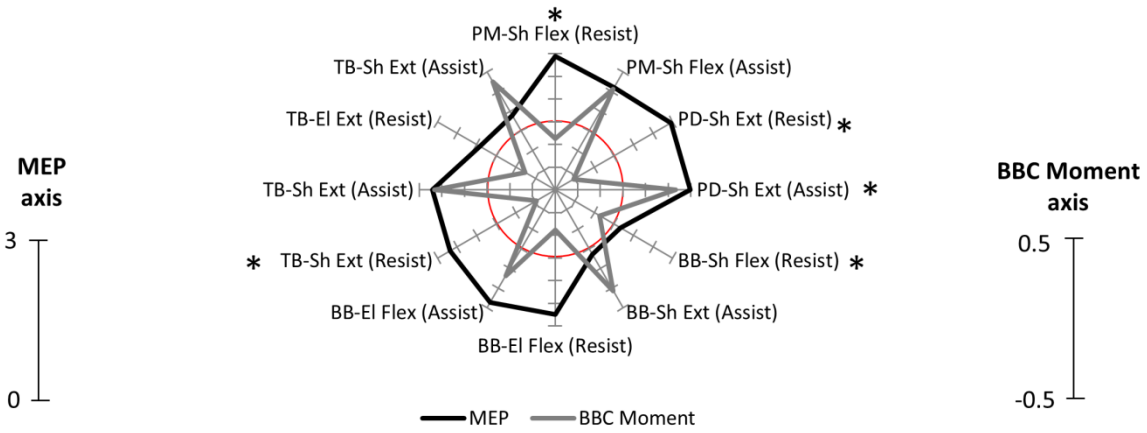


Figure 4.10. Polar plot of the mean MEP amplitude and bone on bone contact moment amplitude used in the correlation analysis. The black line indicates the mean MEP amplitude and the grey line indicates the bone on bone contact (i.e., BBC) moment mean amplitude for each correlation. BBC moment values in the red circle are negative and therefore, *resistive*, while value outside the red circle are positive and therefore, *assistive*. Each point of the polar plot is labelled based on the MEP muscle and BBC moment direction. In each label, the first acronym indicates the muscle that the MEP was recorded from (e.g., PM = pectoralis major), the second label indicates the direction of the net moment when the MEP was recorded (e.g., Sh Flex = shoulder flexor moment), and the word in the bracket indicates whether the BBC moment was in the same (i.e., Assist) or opposite (i.e., Resist) direction of the net moment. An asterisk indicates whether the correlation was significant ($p < 0.05$) between the MEP and the BBC moment.

Table 4.3. Correlational analysis of BBC moment amplitude and MEP amplitude. The MEP muscle column indicates which muscle the MEP was recorded from. Net moment direction indicates that MEPs were only used when the net moment was in the stated direction and when the BBC moment was in the stated direction (i.e., opposite/*resistive* or same/*assistive*).

Net Moment Direction	MEP Muscle	BBC Moment Direction	
		Resistive	Assistive
Shoulder Flexor	Pectoralis Major	r =-0.446, p <0.0001 *	r = 0.107 p = 0.068
Shoulder Extensor	Posterior Deltoid	r = -0.215 p =0.010 *	r = -0.189 p = 0.001*
Shoulder Flexor	Biceps Brachii	r =-0.214 p = 0.035*	r = 0.038 p = 0.522
Elbow Flexor	Biceps Brachii	r =0.016 p = 0.860	r =0.033 p = 0.617
Shoulder Extensor	Triceps Brachii	r =-0.303 p <0.0001 *	r = -0.023 p = 0.696
Elbow Extensor	Triceps Brachii	r = -0.155 p = 0.117	r = -.024 p = 0.657

Since there was an inverse relationship between corticospinal output and *resistive*, but not *assistive*, BBC moments, we sought to determine if MEPs were greater in the *resistive* versus *assistive* condition. We performed a *t*-test on all MEPs during *assistive* versus *resistive* conditions, using the dependent measure of MEP ratio. The MEP ratio was defined as $MEP_{ratio} = \frac{MEP_{Normalized}}{Rxn\ Moment\ Amplitude}$ and calculated for each individual. This approach allowed us to compare MEP amplitude across all muscles while the BBC moment amplitude was controlled. The data, shown in *Figure 4.11*, indicates that MEPs were indeed larger when they were elicited in the *resistive* versus *assistive* conditions ($t_{(95)}$ = 2.086, p = 0.039, d = 0.365) regardless of BBC moment amplitude.

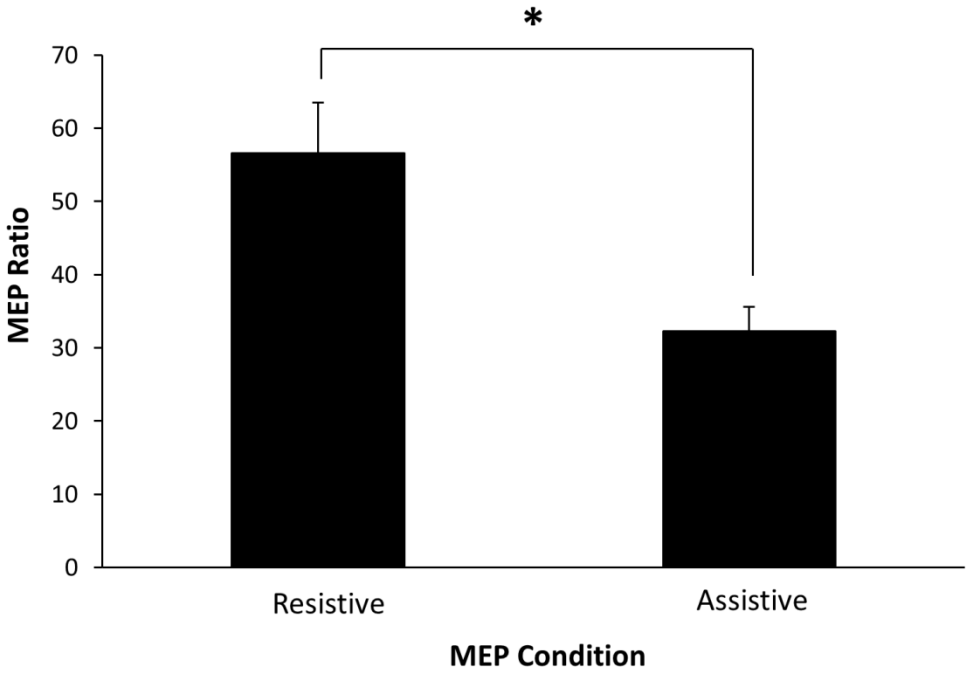


Figure 4.11. MEP ratio in Resistive and Assistive BBC moment conditions. MEP ratio was increased in the *resistive* BBC moment condition in relation to the *assistive* BBC moment condition. Asterisk indicates a significant difference ($p < 0.05$).

4.6 Discussion

The present study investigated whether corticospinal output to upper arm muscles is influenced by the effects inertia and BBC moments have on shoulder and elbow joint rotations, and whether surround inhibition may be an underlying mechanism that allows for inertial effects and BBC moments to contribute to joint motion. During planar arm movements to targets involving unique combinations inertial effects and BBC moments that would *resist* and *assist* the intended joint motion, we expected that corticospinal output to certain muscles would be increased and decreased, respectively. Our study revealed that inertial effects and BBC moments (i.e., *assistive* or *resistive*) modulates

corticospinal output to muscles of the upper arm during a wide variety of complex multi-joint movements. Further, the data suggest that surround inhibition may not participate in the ability of humans to use inertial effects and BBC moments to their advantage to perform complex multi-joint movements. Last, prior to the onset of the movement, corticospinal output was modulated depending on the expected inertial effects and direction of BBC moments, but only for certain muscles or movement types. In sum, the activity within M1 is dependent on the effects of inertia and BBC moments to joint rotation prior to and during multi-joint movement.

Corticospinal output was similar in the two pre-movement phases (i.e., PMP and EOP) such that MEP amplitude differed across target locations for BB, PM, and PD. Previous evidence suggests a relationship between the upcoming *resistive* BBC moments and increased corticospinal output (Gritsenko et al., 2011). The present study was built upon these findings and examined how inertia and BBC moments that *resisted* and *assisted* the primary action of BB, TB, PM, and PD influenced their own corticospinal output prior to and also at the onset of muscle activity. To do so, participants performed movements to targets similar to the 'whipping' and 'reaching' movements performed by Hollerbach & Flash (1982) –a pivotal research finding highlighting the importance of BBC moments in human motor control (Hollerbach & Flash, 1982). During the pre-movement phase, we observed an increase in corticospinal output to muscles when movements had to overcome inertia at both joints and the BBC moment would *resist* the primary action of the muscle. For example, MEPs in BB and PD were largest to targets where BBC

moments would *resist* the intended joint rotations (i.e., for BB, target S_FE_F and for PD, target S_EE_E). Such increases in corticospinal output may act to overcome the *resistive* effects of inertia and the BBC moments occurring at the shoulder, elbow or both joints. One peculiarity was the observation that TB, unlike the other bi-articular muscle tested (i.e., BB), was not modulated by target location and therefore not likely associated with the upcoming effects of inertia and BBC moments at either joint. In the present study, the target locations that required primarily BB activity are typical outward reaching movements performed on a daily basis (i.e., targets S_FE_F, S_FE_0, S_FE_E), while targets that required primarily TB activity were less familiar reaching movements (i.e., targets S_EE_E, S_EE_0, S_EE_F). This unfamiliarity of the target locations may be driving the differences observed between bi-articular muscles. In support of this statement, it is evident that people learn to use BBC moments to their advantage as they become more proficient at a task (Bernstein, 1967; Schneider, Zernicke, Schmidt, & Hart, 1989; Schneider & Zernicke, 1989).

For the movement phase, the data was transformed from target space to net moment space by assigning BBC moments as *assistive* versus *resistive* as determined by the direction of the BBC moment with respect to the net moment at that joint, as seen elsewhere (Asmussen et al., 2014; Dounskaia, Ketcham, & Stelmach, 2002; Sainburg & Kalakanis, 2000), based on the actual movement profiles obtained in individuals (see *Figures 4.8* and *4.9*). This approach revealed significant correlations between corticospinal output and the magnitude of the BBC moment when it *resisted* the net moment direction and primary

action of the muscle, but only rarely when the BBC moment was *assistive*. Specifically, as the *resistive* BBC moment amplitude at the shoulder became larger (i.e., more negative) there was an increase in MEP amplitude for the mono-articular and bi-articular muscles of the upper arm. In contrast to the relationship between corticospinal output and BBC moments at the shoulder, we found no significant relationship between elbow BBC moments and corticospinal output to BB and TB. Previous research demonstrated that BBC moments at the elbow correlated with corticospinal output to these muscles (Gritsenko et al., 2011). Although these data are not in agreement with Gritsenko et al., the divergence may be attributed to target locations. First, in our study, we used targets that required less familiar combinations of shoulder and elbow flexion/extension (i.e., targets $S_E E_E$, $S_E E_0$, $S_E F_E$), while Gritsenko and colleagues' targets required outward reaching movements that are performed on a daily basis. Second, the target location in Gritsenko et al., that displayed dependence of corticospinal output on *resistive* BBC moments was never tested in our study. Both the present study and Grisenkio et al., have demonstrated that during movement, corticospinal output is able to account for increased *resistive* BBC moments. However, it may be that the magnitude of this relationship is dependent on the joint, target location, and/or skill level when performing the task. In sum, the data indicate a dependence of corticospinal output on the contributions of inertia and BBC moments to joint rotations both prior to and during movement and that the output from M1 accounts for the mechanical interaction from inter-connected segments during planning and execution of multi-joint movements.

Surround inhibition acts during movement preparation to reduce neural output to hand muscles that are in the 'surround' of muscles involved in a task (Sohn & Hallett, 2004; Beck & Hallett, 2011; Beck & Hallett, 2010; Beck et al., 2009; Beck et al., 2008; Richardson et al., 2008; Voller et al., 2006; Voller et al., 2005). We hypothesized that surround inhibition would exist in upper limb muscles uninvolved when reaching to specific targets (see Table 4.1). In contrast, surround inhibition did not exist in the majority of muscles tested suggesting that this mechanism does not act during multi-joint movements and/or is restricted to hand muscles where fine fractionated movements are required. An alternative explanation is that the limb mechanics in our task did not allow for muscles to be completely uninvolved in the task since rapid acceleration and deceleration of both limb segments were required to successfully achieve the targets and, therefore, agonist and antagonist muscles would be 'prepared' to be involved in the task. Although our study did not reveal surround inhibition during multi-joint movements, we cannot rule out its role during complex movements. Future studies testing surround inhibition during multi-joint movements should ensure that the muscle tested does not have any involvement throughout the entire task (i.e., decelerates the limb, stabilizing the joint, or is a synergist) or train participants to keep the muscle uninvolved throughout the movement (Kassavetis et al., 2012; Sugawara et al., 2012).

Humans gravitate towards movement that inertia and BBC moments *assist* but not *resist* joint rotations (Wang & Dounskaia, 2012; Goble et al., 2007; Dounskaia et al., 2002; Dounskaia et al., 1998; Dounskaia et al., 2002; Dounskaia, 2005; Dounskaia, 2010;

Asmussen et al., 2014; Dounskaia & Wang, 2014; Schneider et al., 1989; Sainburg & Kalakanis, 2000). In the present study we have shown that larger *resistive* BBC moments are associated with larger MEPs and relatively larger MEPs occur in *resistive* versus *assistive* conditions. Such large MEPs may cause increased 'noise' in the nervous system thereby hindering the ability to achieve movement goals. According to optimal feedback control and also minimized variance theory, a larger control signal can increase the 'noise' in the system and therefore, affect the task goal (Harris & Wolpert, 1998; Todorov & Jordan, 2002; Scott, 2004). Hence, it is beneficial to perform movements with reduced 'noise' to enhance task success. In the present study, the large MEPs associated with *resistive* BBC moments would therefore increase 'noise' in the nervous system. An effective control strategy would be to avoid such movements, and, rather opt for those involving lower neural cost/lower neural noise that accompany *assistive* BBC moments. We have shown that BBC moments that *resist* the net moment at a joint require a larger neural cost to perform. This may be one explanation for the human preference to perform movements that allow inertia and BBC moments to *assist* joint rotation.

The finding that corticospinal output is modulated by the amplitude and direction of the BBC moment (i.e., *resistive* versus *assistive*) lends strong support to the leading joint hypothesis (Dounskaia, 2005; Dounskaia, 2010). This hypothesis states that, during effective multi-joint movement control, one joint 'leads' the movement under 'active' control, while the other inter-connected joints 'trail' and use *assistive* BBC moments to aid in joint rotation. In the present study, we observed that modulation of corticospinal

output occurred mainly at the shoulder joint, and when BBC moments *resisted* motion at that joint. In the reaching movements studied, the shoulder was the 'leading' joint, while the elbow was the 'trailing' joint. Our study supports this leading joint hypothesis, as it was necessary for corticospinal output to 'actively' control the leading shoulder joint and properly modulate M1 output in relation to the *resistive* BBC moments, while corticospinal output did not relate to the BBC moment at the elbow. Further, despite our experimental manipulation designed to create *resistive* BBC moments at both joints, some participants opted to avoid this type of movement strategy (*Figure 4.8* and *4.9*). In our study and Gritsenko and colleagues' study, the corticospinal system modulated its output to the 'leading' shoulder joint. A future study measuring corticospinal output to muscles controlling the elbow when it is the 'leading' joint and the wrist or shoulder is the 'trailing' joint would further confirm the hypothesis of co-occurring increased corticospinal output and *resistive* BBC moments at the 'leading' joint.

The control of inertial effects and BBC moments to joint rotations is essential to performing effective movements. Individuals with cerebellar ataxia exhibit ineffective control of these inertial effects and BBC moments that creates errors during single- and multi-joint movements (Bastian et al., 1996; Bastian et al., 2000; Boose, Dichgans, & Topka, 1999; Topka, Konczak, Schneider, Boose, & Dichgans, 1998). Similarly, children with Developmental Coordination Disorder, a disorder suggested to involve compromised cerebellar functionality (Cantin, Polatajko, Thach, & Jaglal, 2007; Bo, Bastian, Kagerer, Contreras-Vidal, & Clark, 2008; Jongmans, Smits-Engelsman, & Schoemaker, 2003;

Smits-Engelsman & Van Galen, 1997; Smits-Engelsman, Niemeijer, & Van Galen, 2001; O'Hare & Khalid, 2002), demonstrate impaired modulation of BBC moments, resulting in poor motor control and performance during one-handed catching (Asmussen et al., 2014). Further, loss of proprioception is associated with improper control of BBC moments that results in erroneous goal-directed reaching movements (Sainburg et al., 1995). The converging evidence suggests a critical role for the encoding of BBC moments by the cerebellum (Bhanpuri, Okamura, & Bastian, 2013; Kawato & Gomi, 1992; Bhanpuri, Okamura, & Bastian, 2014; Boisgontier & Swinnen, 2014). We suggest that M1 is participating in the modulation of BBC moments via interactions with the cerebellum by a spino-cerebellar, cerebello-thalamo-cortical loop. If true, it could be that, typically the CNS understands that inertial effects and BBC moments that *resist* joint motion cause increased neural cost and noise in the control signal and therefore, learns to perform movements with more *assistive* BBC moments and inertial effects (Schneider et al., 1989; Schneider & Zernicke, 1989). However, if somatosensory input, the cerebellum, or M1 functioning is compromised, these neural structures may not realize the detrimental effects of *resistive* BBC moments and inertial effects and, therefore, continue to perform poorly coordinated movements with ineffective control of moments from inter-segmental forces. If true, future neural rehabilitative interventions for clinical populations that exhibit poor multi-joint movement control should be aimed at enhancing function in this spino-cerebellar, cerebello-thalamo-cortical loop. To support this potential implication, transcranial direct current stimulation over cerebellum can modulate the long latency stretch reflex response (Grimaldi & Manto, 2013), a neural circuit that is able to properly

modulate cortical output based on complex features of multi-joint movements. Excitatory and inhibitory neural plasticity protocols targeted over M1, primary somatosensory cortex, or cerebellum could provide a novel neural rehabilitation intervention that could enhance modulation of inertial effects and BBC moments on joint rotation, ultimately improving multi-joint movement control.

4.6 References

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Appendix 1: Anthropometry

Anthropometric data was calculated for each participant. Participants were weighed and the upper arm, forearm, and hand segment was measured. This information was used to determine the segment length, segment center of mass, and location of segment center of mass using equations from Winter (2009).

Upper arm:

$Segment\ Center\ of\ Mass = 0.028 * M;$

$Center\ of\ Mass\ Location = 0.436 * L_{proximal}$

Forearm:

$Segment\ Center\ of\ Mass = 0.016 * M;$

$Center\ of\ Mass\ Location = 0.430 * L_{proximal}$

Hand:

$$Segment\ Center\ of\ Mass = 0.006 * M;$$

$$Center\ of\ Mass\ Location = 0.506 * L_{proximal}$$

$Where,$
$M = the\ total\ mass\ of\ the\ participant$
$L = the\ length\ of\ the\ segment\ of\ interest$
$L_{proximal} = length\ of\ the\ segment\ in\ relation\ to\ the\ proximal\ end$

Appendix 2: Calculation of muscle, BBC and net moment

$$S_{Muscle} = \left[\left(I_U + m_U {c_U}^2 + I_F + m_F\left({l_U}^2 + {c_F}^2 + 2 l_U c_F \cos\theta_E\right)\right)\alpha_S\right] + \{(I_F + m_F {c_F}^2 + m_F l_u c_F \cos\theta_E)\alpha_E - (m_F l_U c_F \sin\theta_E){\omega_E}^2 - (2 m_F l_U c_F \sin\theta_E)\omega_S \omega_E\}$$

$$E_{Muscle} = [(I_F + m_F {c_F}^2)\alpha_E] + \{(I_F + m_F {c_F}^2 + m_F l_U c_F \cos\theta_E)\alpha_S + (m_F l_U c_F \sin\theta_E){\omega_S}^2\}$$

$Where,$
$I_U = moment\ of\ inertia\ of\ the\ upper\ arm$
$I_F = moment\ of\ inertia\ of\ the\ forearm$
$m_U = mass\ of\ the\ upper\ arm$
$m_F = mass\ of\ the\ forearm$
$c_u = center\ of\ mass\ location\ of\ the\ upper\ arm\ in\ relation\ to\ the\ shoulder\ joint$
$c_F = center\ of\ mass\ location\ of\ the\ forearm\ in\ relation\ to\ the\ elbow\ joint$
$\theta_S = angle\ of\ the\ shoulder\ joint$
$\omega_S = angular\ velocity\ of\ the\ shoulder\ joint$
$\alpha_S = angular\ acceleration\ of\ the\ shoulder\ joint$
$\theta_E = angle\ of\ the\ elbow\ joint$
$\omega_E = angular\ velocity\ of\ the\ elbow\ joint$
$\alpha_E = angular\ acceleration\ of\ the\ elbow\ joint$
$S_{Muscle} = muscular\ moment\ at\ the\ shoulder\ joint$
$E_{Muscle} = muscular\ moment\ at\ the\ elbow\ joint$

Note: [ ] indicates the equation to calculate the Net Moment at each joint and { } indicates the equation to calculate the BBC Moment at each joint. Shoulder and elbow angles are defined in *Figure 4.1*.

5.0 Chapter 5: General Discussion

5.1 General Discussion

The overarching theme of the dissertation was task-dependent modulation of corticospinal descending output. Based on this general theme, I sought to answer three main questions. First, is corticospinal descending output modulated prior to and during movement and, is this modulation dependent on the movement phase? Second, does the corticospinal descending output depend on muscle involvement in the task? Third, how do cortical circuits contribute to corticospinal descending output modulation during movement and what are the neural mechanisms that mediate these changes?

Over a series of experiments organized into three different studies, I answered these three questions. The following sections provide a summary of how these three studies answered the main questions of the dissertation, followed by a theoretical model consolidating my research findings, limitations of the dissertation, future directions, and clinical applications that may benefit from this work.

5.2 Corticospinal output modulation during movement

Throughout the dissertation, I sought to determine if short-latency afferent inhibition (SAI) can be modulated prior to and during movement, while I also studied if corticospinal output can be modulated prior to and during complex multi-joint movements. In these three studies, corticospinal output was probed at three different phases of performing a movement: 1) between a 'warning' and 'go' cue, 2) after a 'go' cue and up to EMG onset, and 3) after EMG onset until the end of the movement. For the

context of this discussion, *movement preparation* was defined as the period between a 'warning' and 'go' cue, *movement initiation* was defined as the period after a 'go' cue up to EMG onset, and *movement execution* was defined as any time point after EMG onset and the cessation of movement.

5.2.1 Movement Preparation

Corticospinal output was modulated as early as the movement preparation phase. SAI in FDI and ADM was modulated during two different time points of the movement preparation phase. Specifically, SAI was reduced during movement preparation for FDI in both studies, but the effects were not as large for ADM. F-wave and H-reflex measures indicated that these changes were likely cortically mediated because there was no observed change in spinal excitability in this phase. I suggest that these changes in SAI during movement preparation can be explained by somatosensory gating. Evidence from SEP recordings in monkeys indicate that, during movement preparation, somatosensory input is gated in M1 and the premotor cortex; SEPS, however, are not gated at the level of the spinal cord during this phase (Seki & Fetz, 2012). Based on these findings, I propose that the changes in SAI during movement preparation are cortically mediated, either locally in M1 or via a projection from the premotor cortex to local M1 circuitry.

The culmination of evidence indicates that SAI may be non-selectively reduced during movement preparation, and the magnitude of the reduction may be specific to the digit performing the movement. Explicitly, changes in SAI were not as prominent in ADM in

relation to FDI and that the reductions in SAI in FDI were not specific to the type of movement being performed. SAI reductions during movement preparation may have a behavioural significance such that reduced SAI may be essential to lessen the impact of somatosensory driven inhibition on M1, and allow for a muscle to be rapidly engaged in a task.

5.2.2 Movement Initiation

Corticospinal output was modulated during movement initiation. Changes in SAI in FDI and ADM 100 ms after the 'go' cue were measured, while modulation of SAI during EMG onset was examined in FDI, but not ADM. Further, corticospinal output to four upper arm muscles (i.e., BB, TB, PM, and PD) was measured 100 ms after the 'go' cue and during EMG onset. During the movement initiation phases in this dissertation (i.e., 100 ms after the 'go' cue and EMG onset), corticospinal output was probed at points in time that would not allow for re-afference from the ongoing movement to project back to the cortex and be incorporated in the feedback process. Hence, the movement initiation phase was indicative of corticospinal output changes as a result of 'planning' the movement. Compared to the movement preparation phase, more task-relevant changes in corticospinal output were observed. SAI was reduced, or even changed to facilitation, when both FDI and ADM muscles were performing the task, while the corticospinal descending output was even sensitive to changes in the mechanics of the upcoming upper limb movements.

The effects during movement initiation, however, did have their caveats. SAI modulation was larger in FDI compared to ADM and corticospinal output was modulated for some, but not all, upper arm muscles during a variety of multi-joint movements. I suggest that these differences could be driven by differences in digit contribution to hand function (e.g., FDI contribute more to hand function compared to ADM) (Swanson, 1964; Kinoshita, Kawai, & Ikuta, 1995; Kinoshita, Kawai, Ikuta, & Teraoka, 1996; Reilmann, Gordon, & Henningsen, 2001) or simply a result of practice/learning (e.g., BB versus TB corticospinal output modulation)(Schneider, Zernicke, Schmidt, & Hart, 1989; Schneider & Zernicke, 1989). Although there are certain restraints to the conclusions drawn during movement initiation, it appears that the neural output becomes more task-focused as the onset of movement approaches. These task-specific changes in corticospinal output are likely mediated by a combination of supraspinal and spinal mechanisms, as evident from the spinal excitability measures. In monkeys, somatosensory input is gated during movement initiation at a number of sub-cortical loci as well as S1, M1, or premotor cortex in a task-relevant manner (Seki & Fetz, 2012; Fetz, Perlmutter, Prut, Seki, & Votaw, 2002; Seki, Perlmutter, & Fetz, 2009; Seki, Perlmutter, & Fetz, 2003) and similar effects are evident in humans (Starr & Cohen, 1985; Staines, Brooke, & McIlroy, 2000; Tapia, Cohen, & Starr, 1987; Cohen & Starr, 1987). M1 has the ability to control activity within S1 (Canedo, 1997; Lee, Kruglikov, Huang, Fishell, & Rudy, 2013; Aronoff et al., 2010) and is potentially responsible for sensing movement (Naito, 2004). It could be the results observed in this dissertation are a result of M1 controlling its own somatosensory input via a sensory gating mechanism. Therefore, this would allow M1 to dictate its

upcoming task-specific output later in the movement based on its own controlled sensory input.

5.2.3 Movement Execution

Corticospinal output was modified during the movement execution phase and the changes were also made in a task-specific manner. I examined changes of SAI in FDI during a tonic muscular contraction with two types of somatosensory input and corticospinal output directed towards BB, TB, PM, and PD during movements with varying combinations of inertial effects and BBC moments that *assisted* or *resisted* joint rotation. During this movement execution phase, there is enough time for re-afference from the ongoing movement to project back to the cortex and movement-related feedback, from sub-cortical and cortical loci, could influence corticospinal output. Compared to the movement initiation phase, the task-relevant modulation of corticospinal output was more evident during movement execution. Specifically, changes in SAI in FDI were modified differently with combined cutaneous and muscular inputs compared to cutaneous inputs alone. These differences likely emerged because the muscular inputs, via mixed nerve stimulation, were more relevant to performing the index finger flexion task and, therefore, drove the differences in corticospinal output. Further, corticospinal output was dependent on the limbs mechanics during the task such that increased corticospinal output was associated with larger magnitudes of *resistive* BBC moments. Since appropriate scaling of corticospinal output in relation to BBC moments is suggested to be essential to successful task performance, these results further highlighted the task-relevant changes in

corticospinal output during the movement. Although the task specific changes in corticospinal output were more evident during movement execution, the proposed neural substrate of corticospinal output modulation via M1 controlling its own input from S1 is suggested to be similar during movement execution and initiation.

5.2.4 Summary of corticospinal output modulation during movement

In sum, corticospinal output is modulated both prior to and during movement. These modulations are dependent on the movement phase, neural circuitry differences between effectors (i.e., contributions of the 2nd versus the 5th digit to hand control), and skill level. Further, changes in corticospinal output are on a continuum such that more task-relevant modulations are observed as the onset of movement approaches and are even more evident during motor task performance.

5.3 Corticospinal output depends on muscle involvement in a movement

I examined whether SAI functions to prevent unwanted movements in muscles controlling the 2nd and 5th digit and if surround inhibition exists in upper-arm muscles, while performing complex multi-joint movements. Corticospinal output was probed during the movement preparation and movement initiation phase because surround inhibition is strongest (i.e., the most inhibition) as the onset of movement approaches (Sohn & Hallett, 2004; Beck & Hallett, 2011; Beck, Schubert, Richardson, & Hallett, 2009; Beck et al., 2008). SAI and surround inhibition functioned to prevent unwanted muscle activity, but it was dependent on the movement phase.

5.3.1 Movement Preparation

I tested SAI during two movement preparation phases, but surround inhibition per se was not explicitly tested in this phase. Precisely, SAI was tested in a muscle controlling the 2nd digit (i.e., FDI) and a muscle controlling the 5th digit (i.e., ADM) when it was uninvolved in a finger flexion task (i.e., 2nd digit finger flexion was the task for testing SAI in ADM; 5th digit finger flexion was the task for testing SAI in FDI). During movement preparation, enhanced SAI (i.e., more inhibition) was not present and, in fact, there were reductions in SAI in certain muscles during movement preparation. Although SAI was still present in this phase, it appears that, during movement preparation, SAI does not function to selectively reduce neural activity to muscles uninvolved in a task.

5.3.2 Movement Initiation

During movement initiation, SAI was reduced and changed to facilitation when a muscle was involved in the task, but remained intact in muscles that were not involved in performing the movement. This evidence indicates that SAI is a neural circuit that is responsible for reducing corticospinal output to muscles that are not intended to be involved in a motor task, as seen elsewhere (Voller et al., 2006). I also tested surround inhibition during two movement initiation phases (i.e., 100 ms after the 'go' cue and EMG onset) in upper-arm muscles during complex multi-joint movements. It was hypothesized that SI would function to reduce corticospinal output to allow inertia and BBC moments to *assist* the upcoming joint rotation. Primarily, I did not observe SI in

any upper arm muscles during the movement initiation phase. This evidence would suggest that SI does not exist in upper arm muscles when performing multi-joint movements and this neural mechanism is restricted to muscles controlling the hand.

An alternative explanation may also exist such that the mechanics of the task were not set-up to effectively test surround inhibition in the upper arm muscles because the muscles tested were not completely uninvolved in the task. The task required participants to quickly accelerate and decelerate both limbs to successfully achieve the target location. It could be that, during movement preparation, neural output to upper arm muscles, that I suspected to not be involved in the task, were indeed 'preparing' to be involved. For instance, during shoulder extension PM would be suspected to not be involved in the task, but this muscle would be necessary to decelerate the upper arm at the end of the movement. This preparation to decelerate the segment may create a neural command that would prevent any surround inhibition to be observed in the study. It is possible, however, that SI could be needed during a similar multi-joint movement that does not require the rapid deceleration. In support of this statement, surround inhibition was present in PD when reaching to target $S_F E_E$ because this muscle was not essential to performing the task. During this movement, the BBC moment from the forearm would *assist* the required net flexor moment at the shoulder and activity of PD would be detrimental to reaching the target. Further, the target was near the end range of motion and it could be that knowing that passive structures (i.e., ligaments) could decelerate the limb when reaching the target caused an inhibition of PD prior to movement. Although

this dissertation primarily did not show surround inhibition during multi-joint movements, we cannot rule out its role during these complex movements.

5.3.3 Summary of corticospinal output dependency on muscle involvement in the movement

In sum, SAI is a circuit that prevents neural output to muscles in close proximity to an active muscle performing an individuated finger movement and may be necessary to focus neural commands during movement initiation, but not movement preparation. SI may function to prevent unwanted muscle activity to upper arm muscles that are not involved in a motor task. To thoroughly answer this question, however, SI and SAI should be tested when participant perform a meticulously designed task for which an upper arm muscle will truly never be involved.

5.4 Cortical circuits and neural mechanisms contributing to corticospinal output modulation prior to and during movement

Throughout the dissertation, I observed how SAI is modulated to allow for individuated finger movement to occur and displayed how corticospinal output alone can be modulated properly to perform effective multi-joint movement control. Further, I examined how SAI may function to prevent unwanted muscle activity and how corticospinal output may be modulated to prevent excessive muscle activity and allow for inertia and BBC moments to *assist* multi-joint movements. The following section will describe some potential neural mechanisms that allow for movement to occur, as well as the mechanisms

that underpin reduced neural output to prevent unwanted (i.e., during individuated finger movement) or excessive muscle activity (i.e., during multi-joint movements). Since the task-specific changes in corticospinal output were selective to the movement initiation and movement execution, the next section applies to these movement phases only.

5.4.1 Focussed neural activity during individuated finger movement

SAI is reduced when a muscle is involved in performing a movement and, in some instances, changes to facilitation. SAI creates inhibition of M1's output as a result of corticocortical projections from S1 or a direct thalamocortical projection to M1 (Tokimura et al., 2000) and is thought to represent central cholinergic activity (Di Lazzaro et al., 2000; Ziemann et al., 2014; Di Lazzaro et al., 2002; Di Lazzaro et al., 2004). When a muscle needs to be involved in the task, SAI may change to a facilitatory circuit because of an interaction between GABAergic inhibitory interneurons. Previous research has shown that, in some instance, SAI turns from inhibition to facilitation in the presence of short-interval intracortical inhibition (SICI) (Alle, Heidegger, Krivanekova, & Ziemann, 2009; Udupa, Ni, Gunraj, & Chen, 2013). SICI is a $GABA_A$ mediated circuit within M1 that acts on a different $GABA_A$ sub-unit in relation to SAI (Di Lazzaro, Pilato, Dileone, Tonali, & Ziemann, 2005; Di Lazzaro et al., 2005; Paulus et al., 2008; Di Lazzaro et al., 2007). It could be that when a muscle needs to be involved in the task, SAI changes from inhibition to facilitation via an interaction of the $GABA_A$ mediated SICI circuit. SAI also changes from inhibition to facilitation in the presence of long-interval cortical inhibition (LICI) (Udupa, Ni, Gunraj, & Chen, 2009). LICI is a $GABA_B$

mediated circuit that acts at a longer time course in relation to SICI (Nakamura, Kitagawa, Kawaguchi, & Tsuji, 1997; McDonnell, Orekhov, & Ziemann, 2006). It could also be that LICI interacts with SAI to allow for focussed muscle activity over a longer time course. Recently, it has been suggested that SAI is facilitated in the presence of short-interval intracortical facilitation (SICF) (Cash, Isayama, Gunraj, Ni, & Chen, 2015). Based on the time course of SICF, I suggest that this circuit could allow for rapid changes in corticospinal output and would seem very beneficial to creating quick changes in motor output specific to the task demands. Although any of these potential interactions could be creating the focussed neural activity, I speculate that the SICF interaction with SAI is mediating the changes because the interaction effects were more reproducible and larger for the SICF-SAI interaction compared to the SICI-SAI or LICI-SAI interaction (Cash et al., 2015; Alle et al., 2009; Udupa et al., 2013; Udupa et al., 2009). This circuit would allow for somatosensory input to interact with local M1 circuitry and rapidly focus neural activity when a muscle is involved in a task.

5.4.2 Focussed neural activity during multi-joint movement

I propose that a similar mechanism is mediating the changes in the corticospinal output observed during multi-joint movement when inertia and the BBC moment *resisted* joint rotation. During multi-joint movement, however, another additional structure is critical. I highlighted the importance of the cerebellum in multi-joint movement control, as suggested elsewhere (Bastian, Martin, Keating, & Thach, 1996; Bastian, Zackowski, & Thach, 2000; Topka, Konczak, Schneider, Boose, & Dichgans, 1998; Kurtzer et al., 2013;

Asmussen, Przysucha, & Dounskaia, 2014). Theoretical models of motor coordination (i.e., optimal feedback control) and empirical data suggests that the long latency transcortical stretch reflex is essential to task-specific feedback control of multi-joint movements (Scott, 2004; Todorov & Jordan, 2002; Pruszynski et al., 2011). The latency of the long latency stretch reflex response would give enough time for somatosensory input to pass through the cerebellum and back to M1, as suggested elsewhere (Pruszynski & Scott, 2012). It could be that proper scaling of corticospinal output during multi-joint movement is driven by the same interactions of somatosensory input within M1, previously discussed for finger movements, except that cerebellar inputs can further scale the corticospinal output from M1. In support of this statement, somatosensory input to M1 changes from inhibition (i.e., with a ~20-28 ms ISI) to facilitation (i.e., with a >30ms and <100ms ISI) (Devanne et al., 2009; Fischer & Orth, 2011), which would overlap the same time course as the long latency stretch reflex processing in M1 and could be driven by cerebellar inputs. Further, stimulation of cerebellum prior to M1 stimulation causes facilitation of corticospinal output at a very short ISI (i.e., 3ms) (Terao & Ugawa, 2002; Iwata et al., 2004; Iwata & Ugawa, 2005), cerebellar damage reduces intra-cortical facilitation (Liepert et al., 1998), plasticity inducing protocols over the cerebellum modulates SAI (Di Lorenzo et al., 2013), and damage to the cerebellum affects early processing of somatosensory input within S1 (Restuccia et al., 2001). Overall, focussed neural activity during single- and multi-joint movements may be driven by a coordination of somatosensory inputs with the cerebellum and local circuitry within M1.

5.4.3 Preventing unwanted neural activity during movement

SAI remained intact to prevent any unwanted muscle activity during individuated finger movements. SAI appears to be a powerful mechanism that can prevent unwanted muscle activity (Voller et al., 2006). Afferent feedback from muscles that are not involved in the task may project, via S1, to M1 and prevent any unwanted muscle activity during single digit movements. Another mechanism that is also expected to mediate this type of fractionated finger control is SICI (Kujirai et al., 1993; Di Lazzaro et al., 1998). SICI has been shown to increase surround inhibition to further focus neural activity (Beck et al., 2008) and may cause more inhibition of SAI in some instances (Alle et al., 2009). When this SICI circuit is not functioning properly, it causes changes in surround inhibition and could be related to movement problems (Beck et al., 2008). It is likely that a combination of these fast acting inhibitory circuits (i.e., SAI and SICI) allows for the control of unwanted muscle activity. Although not explicitly tested, I suspect that the same mechanism may allow for reduced neural output when inertia or BBC moments *assist* the intended joint rotation during multi-joint movements with an additional role of the cerebellum. To support this hypothesis, cerebellar stimulation not only facilitates M1 output, it also inhibits its output depending on the stimulation parameters (Ugawa et al., 1991; Iwata & Ugawa, 2005). The prefrontal cortex (Knight, Staines, Swick, & Chao, 1999), premotor cortex, and M1 are all able to gate sensory input before M1 sends its output (Seki & Fetz, 2012). I speculate that these frontal areas during movement are able to pre-emptively send collaterals to sensory areas of the cortex and sub-cortical loci and

therefore, allow M1 to control its own sensory inputs. This would allow M1 to properly increase or decrease its motor outputs depending on the muscle's involvement in the task.

Overall, effective processing of somatosensory input via the cerebellum and frontal areas of the cortex allows for successful movement performance. This orchestration of motor output and controlled sensory input would allow M1 to finely control both wanted and unwanted movement and create effective single- and multi-joint movements.

5.5 Model of focussed neural activity

The following section describes a neural model that would explain the research findings from this dissertation. The proposed structures and neural mechanisms in this model are not the only elements contributing to the results in this dissertation, but I suggest that these are the *most influential* factors driving somatosensory-motor processing during movement. The model is primarily focussed on S1 and M1 connectivity and function and how other cortical and sub-cortical loci contribute to this S1-M1 processing.

5.5.1 Model for increased neural activity for muscles involved in a task

Figure 5.1 depicts the circuitry involved in increasing output from M1 when muscles are involved in a task. Within M1, *Figure 5.1* displays three excitatory interneurons projecting onto a common corticospinal output neuron that sends an excitatory input to alpha motor neurons controlling the muscle of interest. This model describes what happens with a single TMS pulse, as proposed elsewhere (Di Lazzaro et al., 2004;

Ziemann & Rothwell, 2000). I suggest that this circuit can be facilitated when a muscle needs to be involved in the task via somatosensory input. An excitatory input from S1, onto excitatory interneurons located in the superficial layers of M1, would increase activity to the intended muscles involved in a task (*Figure 5.1*, pathway 2). In support of this connectivity, there is evidence that electrical stimulation of S1 can cause EPSP onto interneurons located in the superficial layers of M1 (Ghosh & Porter, 1988) and tetanic stimulation of S1 can create long-term potentiation in M1 (Sakamoto, Porter, & Asanuma, 1987; Iriki, Pavlides, Keller, & Asanuma , 1989). In humans, SAI interacts with SICF to create facilitation of output to the targeted muscle (Cash et al., 2015). This facilitation is thought to occur via an excitatory input from S1 to the more indirect interneurons located in the superficial layers of M1 (Di Lazzaro & Ziemann, 2013). In this dissertation, SAI was reduced, or changed to facilitation, when it was involved in a task. Further, corticospinal output was increased with *resistive* BBC moments. This connectivity in *Figure 5.1* would explain the somatosensory driven increased corticospinal output when a muscle needs to be engaged in the intended movement or when a *resistive* BBC moment is 'sensed' and increased corticospinal is necessary for successful task performance.

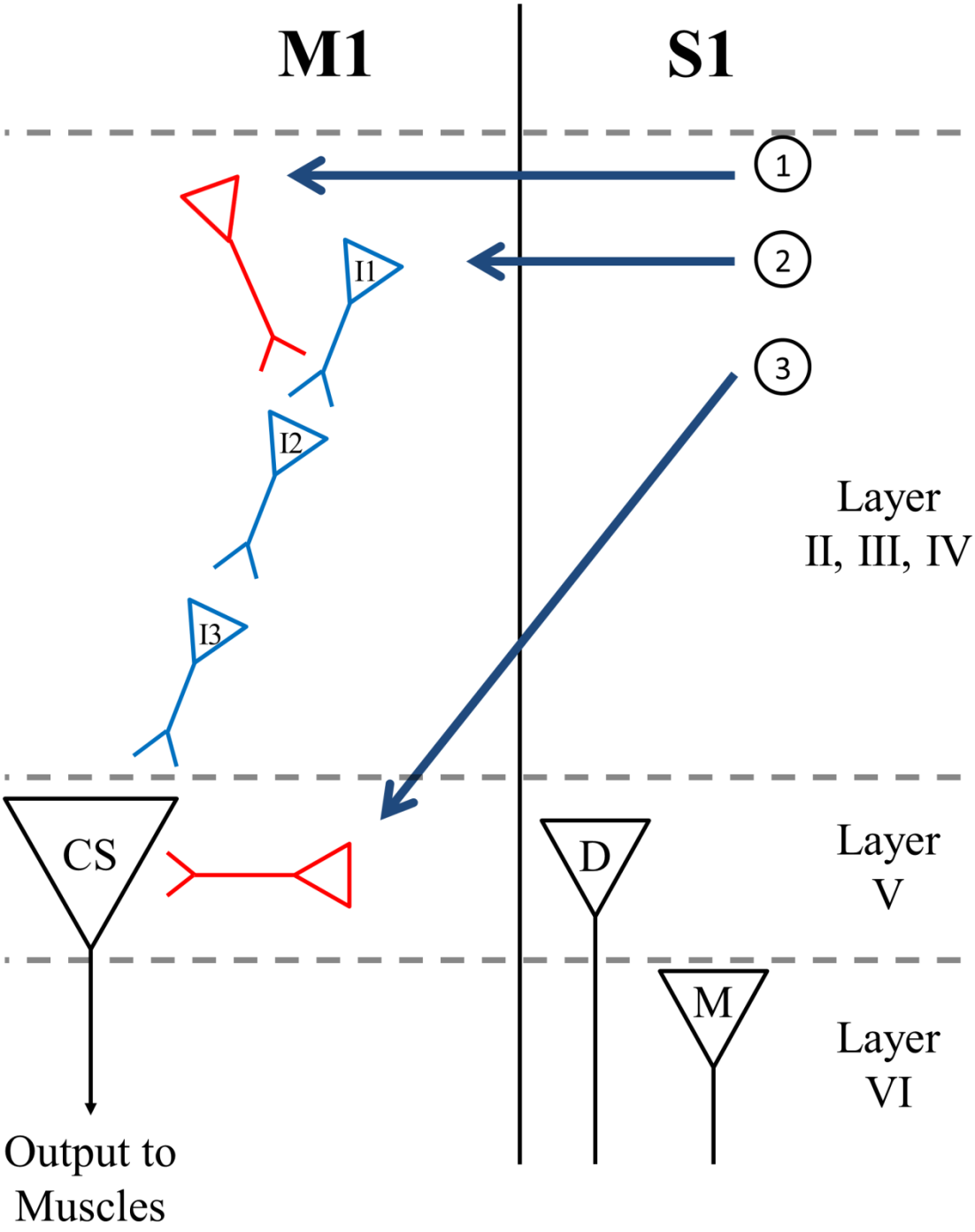
M1
S1
1
2
3
I1
I2
I3
Layer
II, III, IV
CS
D
M
Layer
V
Layer
VI
Output to
Muscles

Figure 5.1. Model for focussed neural activity. 'CS' represents the corticospinal output neuron to the target muscle by a TMS pulse. The blue interneurons indicate excitatory inputs, while the red interneurons indicate inhibitory input. I1, I2, and I3 depict I1-wave, I2-wave, and I3-waves, respectively, from a TMS pulse. 'D' represents the driver neuron from S1 and 'M' represents the modulatory neuron from S1. '1' represents the inhibitory pathway arising from an excitatory input from S1 to the superficial layers of M1. '2' depicts the facilitatory pathway via an excitatory input from S1 to an excitatory interneuron in the superficial layers of M1. '3' displays the inhibitory pathway mediated by an excitatory input from S1 to an inhibitory interneuron in the deeper layers of M1.

5.5.2 Model for decreased or modulated neural activity for muscles not involved in a task

Figure 5.1 also depicts the circuitry involved in decreasing or modulating output from M1 when muscles are not involved in a task. Within M1, the excitatory interneuron connection to the corticospinal output neuron can be inhibited or reduced. An excitatory input from S1 can project onto an inhibitory interneuron within the superficial (*Figure 5.1*, path 1) or deep layers (*Figure 5.1*, path 3) of M1 (Aronoff et al., 2010; Ferezou et al., 2007). I suggest that the deep layer inhibition can function to mask or shunt any facilitation driven by the superficial layers, while the role of the superficial layer inhibition may be to further reduce neural activity to ensure no excitatory input is projected to a muscle not involved in a task. In support of this connectivity, electrical stimulation from S1 typically causes IPSP within M1 (Ghosh & Porter, 1988). SAI is thought to function via an excitatory input from S1 onto inhibitory interneurons within the deep layers of M1 (i.e., path 3), as suggested elsewhere (Cash et al., 2015). I suggest that SAI mediated in the deep layers allows any input from the later excitatory interneurons to be 'masked' and prevent unwanted muscle activity. Further, SAI, in some

instances, causes increased inhibition within local M1 circuitry (Alle et al., 2009) and would be similar to *Figure 5.1* path 1. SAI remained intact to prevent unwanted muscle activity and I suggest that path 1 and 3 in *Figure 5.1* would drive this inhibition. Corticospinal output was reduced when inertia and BBC moments *assisted* joint motion and this modulation may have been driven by path 1's inhibition scaling path 2's excitatory activity. Overall, the level of inhibition, or reduced neural activity in M1, can be determined by the circuitry displayed in *Figure 5.1*.

5.5.3 Model for other cortical influences on somatosensory-motor processing

The schematic in *Figure 5.2* describes how other cortical areas may influence the circuitry displayed in *Figure 5.1*. Although the connectivity between cortical and sub-cortical structures is very elaborate, I suggest that the pathways depicted are *primarily influencing* the somatosensory-motor processing (i.e., M1-S1 connections) described above in *Figure 5.1*. The structures involved in this model are the basal ganglia (BG), cerebellum (Ce), M1, pre-frontal cortex (PFC), pre-motor cortex (PMC), posterior parietal cortex (PPC), S1, the thalamus, and the thalamic reticular nucleus (TRN).

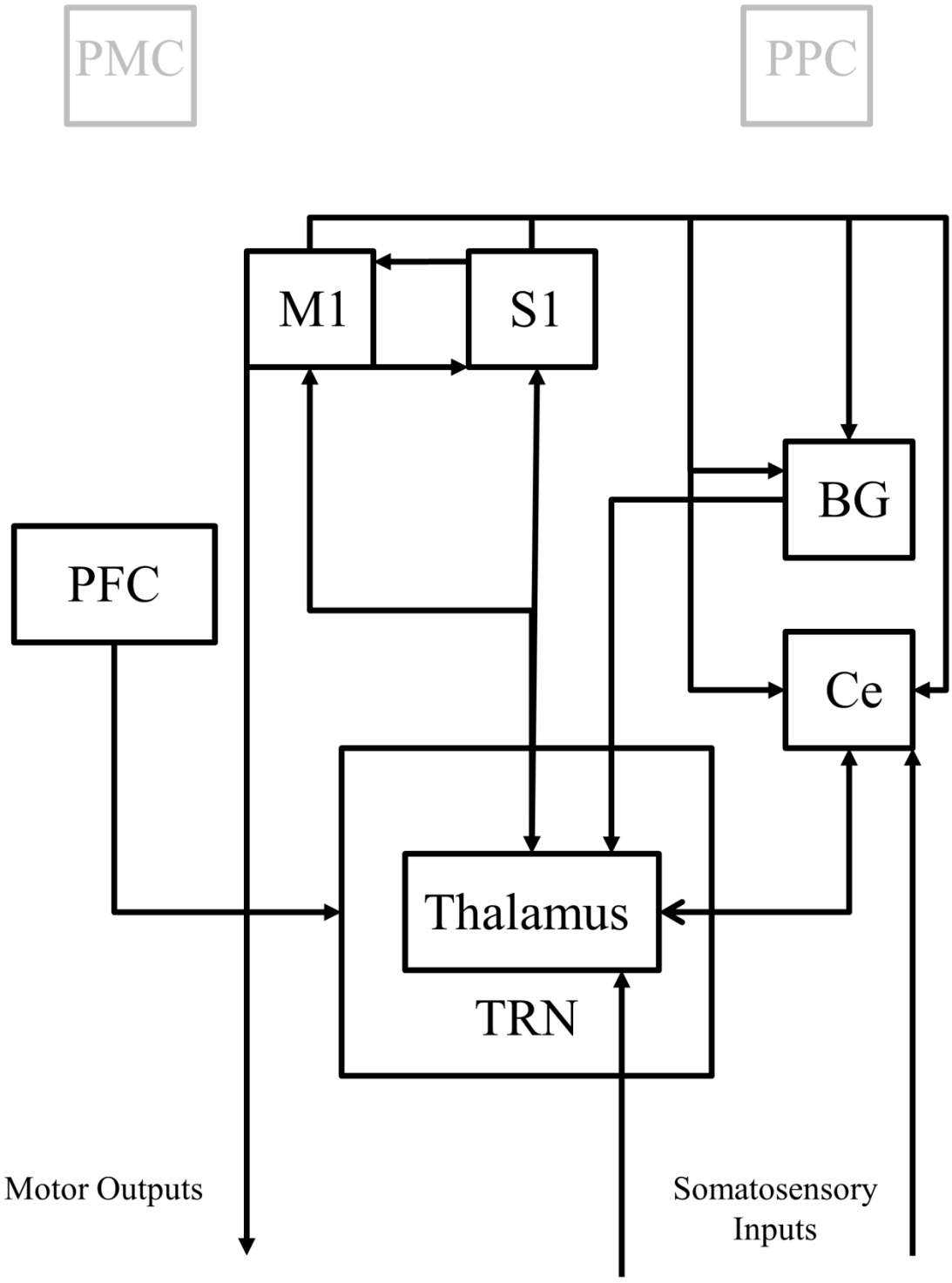
PMC
PPC
M1
S1
BG
PFC
Ce
Thalamus
TRN
Motor Outputs
Somatosensory
Inputs

Figure 5.2. Other cortical structures mediating S1-M1 processing. BG = basal ganglia, Ce = cerebellum, PFC = pre-frontal cortex, PMC = premotor cortex, PPC = posterior parietal cortex, TRN = thalamic reticular nucleus. PFC projects to TRN and modulates input to the cortex via the thalamus. S1 receives inputs from M1 and thalamus and reciprocally sends outputs to M1 and the thalamus. M1, and S1, completes a loop with the basal ganglia and thalamus as well as a loop with the cerebellum and the thalamus. PMC and PPC also play a complicated role in this processing that is beyond the scope of the model.

5.5.3.1 Pre-frontal cortex, Thalamus, and TRN

The role of the pre-frontal cortex in this model is to modulate input from the thalamus to S1 and M1. The thalamus used to be thought as a passive structure to pass sensory input to the cortex. Recent theories suggest that the thalamus and a structure overlying the thalamus, namely the TRN, play a critical role in influencing what sensory information projects to the cortex (Zikopoulos & Barbas, 2007). The PFC has dense connectivity with the TRN (Zikopoulos & Barbas, 2006). The PFC can send inputs to the TRN and cause both inhibition or disinhibition (i.e., facilitation) of thalamocortical inputs (Zikopoulos & Barbas, 2007). This connectivity between PFC and the TRN would allow task-relevant and task-irrelevant inputs to be enhanced and inhibited, respectively, before projecting to S1 and M1. This PFC-TRN-thalamus circuit has been proposed to be active both during and prior to movement (Brunia, 1993). In this dissertation, I believe that this circuit allowed for somatosensory input to be gated if it was irrelevant to the muscle performing the task, while inputs were enhanced when they were relevant to performing the task. I further suggest that this circuit dictates a very important first step in somatosensory-motor processing that controls which muscles are involved and not involved in a task.

5.5.3.2 Basal Ganglia

The role of the basal ganglia is to control the level of ongoing muscle involvement. A loop connecting M1 and S1 with the basal ganglia and thalamus can focus or prevent muscle activity in a motor task. In this dissertation, SAI was reduced or changed to facilitation when a muscle needed to be involved in the task. I suggest that the cortex increases activity in the 'direct pathway' under this condition. In the direct pathway, inputs from the cortex excite the striatum. The striatum sends inhibitory inputs to the GPi and the GPi sends inhibitory inputs to the thalamus. When the cortex excites the striatum, the inhibition from GPi to the thalamus is disinhibited from the striatal input and causes an increased thalamocortical input. This increased thalamocortical input increases activity of M1 output and hence, increased activity to alpha motor neurons (Mink, 1996). When SAI remained intact and the muscle was not involved in the task, I suggest that the cortex increases activity in the 'indirect pathway'. In the indirect pathway, the cortex excites the striatum. The striatum sends an inhibitory input to the GPe and the GPe sends an inhibitory input to the STN. When the cortex excites the striatum and the STN is disinhibited by the striatal to GPe input. The STN sends an excitatory input to the GPi and since the GPi inhibits the thalamus, the thalamocortical input is inhibited (Mink, 1996). This reduced thalamocortical input would decrease activity in corticospinal output neurons controlling muscles not involved in a task, as seen in surround inhibition (Beck & Hallett, 2011). Therefore, the basal ganglia are able to control/monitor the activity of muscles in a task-dependent manner.

5.5.3.3 Cerebellum

The cerebellum is thought to play a critical role in motor coordination (Bhanpuri, Okamura, & Bastian, 2013; Kawato & Gomi, 1992; Asmussen et al., 2014; Bastian et al., 1996; Bastian et al., 2000; Topka et al., 1998). This model does not intend to describe the complicated intricacies of the cerebellum, as seen elsewhere (Kawato & Gomi, 1992; Wolpert, Miall, & Kawato, 1998), but instead, describe a general role of this structure as it applies to the results of this dissertation. The cerebellum may act as a location to compare the ongoing movement with the predicted movement that is unfolding (Kawato & Gomi, 1992; Blakemore, Frith, & Wolpert, 2001; Blakemore, Wolpert, & Frith, 1998; Blakemore, Wolpert, & Frith, 1999). The cerebellum receives inputs from the cortex that are thought to represent a motor efference copy of the movement. The cerebellum also receives sensory inputs via the thalamus as well as from the spino-cerebellar tract (Canedo, 1997). These inputs from the periphery likely give information to the cerebellum of the actual ongoing movement (Wolpert et al., 1998). If any errors in the movement emerge that are affecting the task goal, the cerebellum may be able to send inputs to S1 and M1. Corticospinal output was increased with *resistive* BBC moments and these BBC moments would cause an error in the task goal if they were not accounted for by M1's output. I suggest that inputs from the cerebellum may act on the circuit described in *Figure 5.1* to both increase and decrease intended and unintended motor activity, respectively, specific to the task goal.

5.5.3.4 Primary Motor and Somatosensory cortices

The complexities of the S1 and M1 connections are already described in *Figure 5.1*. M1 and S1 have dense reciprocal connectivity (Ghosh & Porter, 1988). S1 may be able to dictate how M1 responds to somatosensory input by increasing activity to output neurons depending on the task demands as described in *Figure 5.1*. M1, however, also sends projections to S1 (Aronoff et al., 2010). This connectivity may be necessary for M1 to send its own efference copy to S1 (Hill, Curtis, Moore, & Kleinfeld, 2011) and control its own somatosensory afferents. This connectivity would allow M1 to dictate how inputs coming from S1 ultimately affect the corticospinal outputs from M1. S1 itself can also control which inputs it receives from the cortex. Via assistance from PFC, modulatory inputs from layer 6 of the cortex can project back to the thalamus and further disinhibit and inhibit inputs coming from the periphery (Zikopoulos & Barbas, 2007) (see *Figure 5.1*). This would allow S1 to control inputs that are relevant to the task (i.e., muscle involved), while ignoring inputs that are irrelevant (i.e., muscle not involved). S1 also contains driver neurons within layer 5 of the cortex (Zikopoulos & Barbas, 2007) (see *Figure 5.1*). These inputs can project back to higher order areas of the thalamus before projecting to higher order sensory processing centers in the cortex such as PPC. PPC, PMC, and secondary somatosensory cortex (S2) are higher order processing areas that have connection between each other, M1, S1, and the thalamus. These areas likely play a role in somatosensory-motor processing, but their roles were not tested in this dissertation and are beyond the scope of the presented model. I suggest that their inputs, however, could act to control the facilitation and inhibition circuits acting within M1 displayed in

Figure 5.1 and influence outputs to the intended muscles necessary for the task. In support of this statement, paired pulse TMS between area 5 and M1 causes facilitation of corticospinal output (Ziluk, Premji, & Nelson, 2010).

5.5.3.5 Summary of Models

Overall, the results of this dissertation are explained by the models presented in *Figure 5.1* and *Figure 5.2*. I suggest that M1 and S1 are housed in an advantageous location to make rapid changes in corticospinal output in a task-specific manner. Other cortical and sub-cortical areas such as BG, Ce, PFC, PMC, PPC, S2, and TRN all play an essential role in somatosensory-motor processing and these inter-connected structures may be able to directly influence the connectivity between S1 and M1 or local connectivity within M1. Ultimately, the end results would be focussed or hindered neural activity depending on the task demands.

5.6 Limitations, Future Directions, and Clinical Applications

The following section describes the limitations, future directions, and clinical applications of each study in the dissertation.

I exhibited task-specific changes in SAI during movement as inferred from differences in this circuit with two types of nerve stimulation (i.e., mixed versus cutaneous nerve stimulation). In this study, I was not able to disentangle the effects of cutaneous versus muscle afferent inputs. Due to equipment limitations, I was able to deliver cutaneous

only or cutaneous and muscle inputs, but not elicit SAI with muscle afferents only. Future work, using microneurography, would be able to disentangle the effects seen in this work and determine if the muscle afferents were driving the task-specific modulation of SAI. This work would have applications to certain movement disorders that include the motor symptom of muscle weakness. For instance, after a stroke, individuals have movement issues (i.e., poor individuated finger movements) likely because of reduced corticospinal output to muscles needed to perform the task (Schieber, Lang, Reilly, McNulty, & Sirigu, 2009). Future plasticity inducing protocols should be aimed at reducing SAI during movement to improve motor symptoms in these individuals. Emerging work has shown some promise in this area for typically functioning individuals (Tsang et al., 2014; Tsang, Bailey, & Nelson, 2015; Quartarone et al., 2006).

I displayed pre-movement changes in SAI in muscles involved and uninvolved in finger flexion tasks with the most prominent effects observed during movement initiation. One limitation was that the changes in SAI could have been driven by the stabilizing role of the other digits while performing the task. In this study, I only had a crude explanation of the mechanics required to perform the finger flexion task. Future studies should have the participant's hand placed in a constraint such that isolated finger flexion can be performed. Because of this constraint, stronger inhibition of the muscles in proximity to the active muscle may be observed because they are not required to stabilize the hand. In support of this requirement, the degree of surround inhibition (i.e., how much inhibition) in certain hand muscles varies across studies (Kassavetis et al., 2012; Beck et al., 2009;

Voller et al., 2005; Sugawara et al., 2012; Voller et al., 2006; Beck & Hallett, 2010; Beck et al., 2008; Shin, Sohn, & Hallett, 2009). These studies fail to give an adequate analysis of the mechanics required to perform the task. It could be that surround inhibition is variable because of the differences in the mechanics of the task across participants and studies. Future research should address these concerns. Further, there was a change from inhibition to facilitation during movement initiation. It was suggested that GABAergic interneuronal interactions mediate the focussed neural activity in the muscle involved in the task, while GABAergic interneurons may mediate the inhibition in muscles not involved in the task. Future pharmaceutical studies involving $GABA_A$ or $GABA_B$ agonists should investigate these effects to determine the underlying mechanisms. This future proposed work will have immediate impact on individuals who exhibit unwanted movements such as dystonia or Parkinson's disease. Plasticity protocols aimed at enhancing SAI in muscles producing unwanted activity during movement would likely show improvements in motor symptoms. In support of this statement, repetitive TMS over M1 and S1 has shown changes in SAI circuitry (Tsang et al., 2014; Baumer et al., 2007; Tsang et al., 2015; Quartarone et al., 2006).

I emphasized how corticospinal output is dependent on the contributions of inertia and BBC moments to joint rotations. Originally, this dissertation was going to explore the role of SAI in controlling upper arm muscle activity during multi-joint movements with varying combinations of *assistive* and *resistive* BBC moments and inertial effects. Because of the complexities of multi-joint movements, further research was required to

understand how corticospinal output in general functions during the different types of multi-joint actions. Given the understanding gained from this information, the experimental paradigm for studying multi-joint movement in this dissertation provides a baseline for understanding how different cortical circuits function to control upper limb muscles during multi-joint movements and uncover the neural correlates of the leading joint hypothesis (Dounskaia, 2010; Dounskaia, 2005; Asmussen et al., 2014). Further, there were some limitations to the conclusions drawn from the multi-joint upper arm movement study. We made the assumption that the roles of the muscles studied were either agonist or antagonist depending on the direction of the net and BBC moments. Muscles do play other roles in multi-joint movements such as providing synergist activity and/or stabilization. Further, muscles may never have been truly uninvolved in the task and therefore, I could not observe surround inhibition in these muscles. Also, not all upper arm muscles were studied, because of methodological limitations, and activation of these other muscles (ex., brachioradialis, brachialis) could have been necessary for coordinating the multi-joint movement. All these factors may be the source of some of the unexplained variance in this study. Future work in this area should develop a link-segment and muscle model of the upper arm to make predictions of the role of certain muscles at certain times during the movement and correspondingly probe corticospinal output to these muscles. This work and future extensions would be beneficial to individuals who have issues with multi-joint movements such as Cerebellar Ataxia, stroke, and Developmental Coordination Disorder. Excitatory and inhibitory plasticity inducing protocols aimed at the cerebellum, S1, or M1 would likely show promise in

improving multi-joint movement control in these individuals. For example, if an individual exhibits the inability to scale corticospinal output to the magnitude of the BBC moments or joint rotation due to inertia, a plasticity inducing protocol over one of these areas should show changes in the circuit depicted in *Figure 5.1* and maybe even a behavioural correlate of effective modulation of muscle activity in relation to BBC moment and inertial effects that contribute to joint rotations.

5.7 Conclusion

In conclusion, this dissertation explored the underlying circuitry mediating finger and upper arm control and how these circuits changed in a task dependent manner. This work examined how these circuits functioned to allow for muscle to be involved in a task, but also how the circuits and mechanisms were responsible for preventing unwanted muscle activity. I have proposed a model for how S1 and M1 are coordinated to allow and prevent muscle activity and how this can occur in a task-specific way. This model can be used as a means for further exploration of motor neurophysiology and guide neural plasticity-inducing protocols for rehabilitation. The largest effect in this dissertation was uncovered when the mechanics of the task were thoroughly explained, suggesting how important this factor is when interpreting results from motor neurophysiology studies. I suggest that a combination of biomechanical and neural models, namely involving TMS, will provide the largest gains in basic human sensorimotor control and clinical sensorimotor neurophysiology.

5.8 References

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After 24 years of jumping over hurdles set up by someone else to obtain accreditation that I have the ability to produce quality work, ironically, I believe that the take home message from my education career can be summed up by the following quote from Robert M. Pirsig's book *Zen and the Art of Motorcycle Maintenance*:

"And what is good, Phaedrus,
And what is not good—
Need we ask anyone to tell us these things?"