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THE EFFECT OF INTERMITTENT THETA BURST STIMULATION ON BICEPS CORTICOMOTOR EXCITABILITY IN NON-IMPAIRED INDIVIDUALS AND INDIVIDUALS WITH TETRAPLEGIA

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A thesis submitted in partial fulfillment of the requirement for the degree of Master of Science in Biomedical Engineering at Virginia Commonwealth University.

by

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Physiological Abbreviations

Ca^{2+}	Calcium
CNS	Central nervous system
FCR	Flexor carpi radialis
FDI	First dorsal interosseous
GABA	γ-aminobutyric acid
LTD	Long-term Depression
LTP	Long-term Potentiation
M1	Primary motor cortex
NMDA	N-methyl-D-aspartate

General Abbreviations

AMT	Active motor threshold
ASIA	American Spinal Injury Association
cTBS	Continuous theta burst stimulation
EMG	Electromyography
iTBS	Intermittent theta burst stimulation
MEP	Motor evoked potential
Mmax	Maximal compound muscle action potential
MSO	Maximum stimulator output
nMEP	Normalized motor evoked potential
RMT	Resting motor threshold
rTMS	Repetitive transcranial magnetic stimulation
SCI	Spinal cord injury
TBS	Theta burst stimulation
TMS	Transcranial magnetic stimulation

Abstract

THE EFFECT OF INTERMITTENT THETA BURST STIMULATION ON BICEPS CORTICOMOTOR EXCITABILITY IN NON-IMPAIRED INDIVIDUALS AND INDIVIDUALS WITH TETRAPLEGIA

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Neuromodulation of the primary motor cortex (M1) in pair with physical therapy may be a promising method for improving motor outcomes after spinal cord injury (SCI). Increased excitability of the corticospinal motor pathways (i.e. corticomotor excitability) has shown to be associated with improved motor learning and skill acquisition. Intermittent theta burst stimulation (iTBS) is a form of non-invasive brain stimulation which can increase corticomotor excitability, as measured by an increase in the amplitude of motor evoked potentials (MEPs). Our long-term goal is to determine if iTBS paired with physical therapy can improve motor re-education of upper limb muscles after tendon or nerve transfer in individuals with tetraplegia. Proximal upper limb muscles, such as the biceps brachii, can be surgically transferred to restore elbow extension. However, the ability for iTBS to increase the corticomotor excitability of proximal muscles such as the biceps, and muscles affected by spinal cord injury is currently unclear. The majority of studies involving iTBS have targeted the first dorsal interosseous (FDI)

in non-impaired individuals. While these studies have found iTBS to increase the amplitude of MEPs, the effects often vary across participants resulting in negative findings group wide. One study which targeted the flexor carpi radialis (FCR), a muscle more proximal than the FDI, found that differences in the resting motor thresholds (RMT) between the FCR and its antagonist muscle (extensor carpi radialis) appeared to determine the efficacy of iTBS. However, these observed effects may not translate to the biceps due to differences in corticospinal control across muscles. Therefore, the purpose of the present studies was to determine the effect of iTBS on the corticomotor excitability of the biceps, as measured by MEP amplitudes, in non-impaired individuals and individuals with tetraplegia. Participants completed three sessions of the protocol, each including sham and active iTBS. Sessions were separated by a minimum of three days to prevent the potential for carry over effects. Participants were instrumented with surface electromyography electrodes on the biceps and its primary antagonist of their dominant arm. The maximal compound action potential (Mmax) was recorded from these muscles for the normalization of MEPs (nMEP). Resting motor threshold (RMT) and active motor threshold (AMT) were then determined by delivering single pulse TMS. MEPs were recorded via single pulse TMS delivered at an intensity of 120% RMT, at intervals before, 10, 20, and 30 min after sham and active iTBS. The iTBS parameters consisted of three pulses presented at 50 Hz, repeated every 200 ms for 2 s at an intensity of 80% of the participant's AMT. Two second bursts were repeated every 8 s for a total of 600 pulses. Single pulse TMS and iTBS were both delivered with a Super Rapid Plus stimulator via a 70 mm figure-of-eight coil (Magstim). No change in nMEP amplitude after either sham or active iTBS was found in the non-impaired group. However, the SCI group showed an increase in nMEP amplitude after active iTBS relative to sham, suggesting an increase in corticomotor excitability. Furthermore, there was no correlation in either group between the changes in nMEP amplitudes and the difference between the RMT of the biceps and its antagonist (triceps brachii). While further research is needed before combinatorial therapies can be achieved, this study suggests that iTBS may be a promising method for improving motor function in those with tetraplegia.

Chapter 1: Introduction

1.1 Neurophysiology of the central nervous system

The central nervous system (CNS) is a complex electrochemical network which is responsible for processing and controlling our bodies' movements (Silva, Sousa, Reis, & Salgado, 2014). The two components that make up the CNS are the brain and the spinal cord. While the brain is responsible for planning each of our body's movements, the spinal cord is the mechanism which transmits this information to the muscles. This transmission is achieved through the billions of cells which make up both the brain and spinal cord, neurons.

1.1.1 Neurons

Neurons are specialized cells capable of receiving, generating, and sending electrical signals known as action potentials (Figure 1). Action potentials produced by neurons are caused by responses to stimuli, which change the resting membrane potential of the neuron. Action potential propagation begins at the post-synaptic terminal, where neurotransmitters bind to receptors on the cell's membrane. Action potential propagation begins at the post-synaptic terminal, where neurotransmitters bind to receptors on the cell's membrane. Two receptors which play a large role in the CNS are the NMDA (N-methyl-D-aspartate) and GABA (γ-aminobutyric acid) ion channels. The NMDA receptor is activated by excitatory neurotransmitters, such as glutamate, which triggers calcium (Ca^{2+}) influx into the cell and increases the potential for signal propagation. The GABA receptors on the other hand are activated by inhibitory neurotransmitters, which increases chloride conductance of the membrane and decreases the potential of signal propagation. If the neurotransmitters are able to induce a positive change in the membrane potential relative to its resting state (depolarization) that meets a certain threshold (i.e., threshold potential), the neuron will generate an action potential. This action potential will then travel from the neuron's cell body and along the axon of the neuron until it reaches the presynaptic terminal. The presynaptic terminal then terminates at its target cell (i.e., other neurons or muscle cells) in what is known as the synapse. At the synapse, the presynaptic terminal releases neurotransmitters which diffuse and then bind to receptors on the post-synaptic membrane of the target cell. Neurons

which form synapses with other neurons are called interneurons, while neurons that form synapses with muscle cells are known as motor neurons.

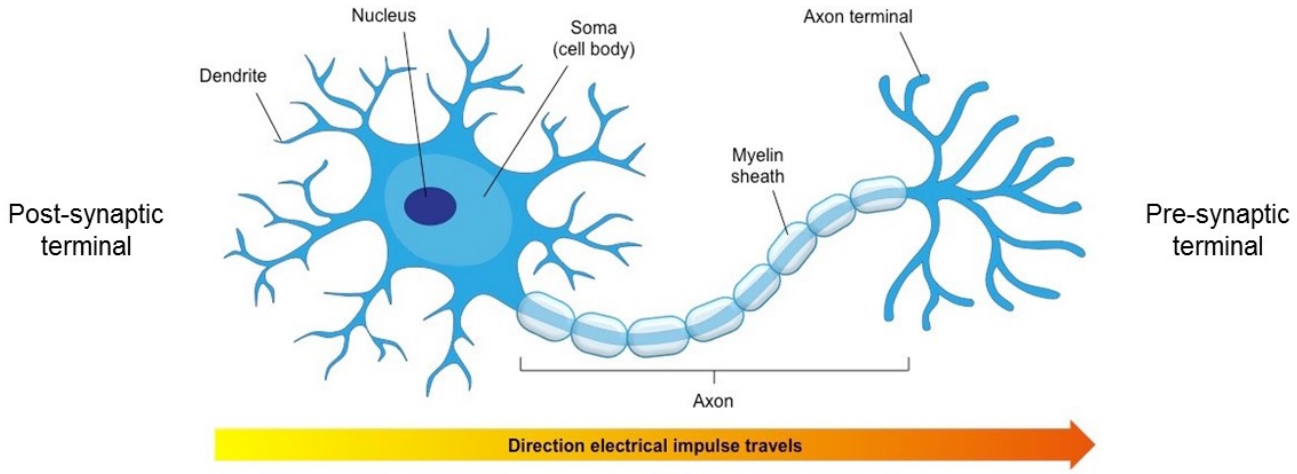

Figure 1. Anatomy of the neuron depicting the direction of signal propagation. (Brett Szymik, 2011)

Motor neurons are those which have their cell body located in the motor cortex region of the brain, brainstem, or spinal cord. Their axons then project to either the spinal cord or directly to muscle fibers (Tortora & Derrickson, 2014). There are two different types of motor neurons: upper motor neurons and lower motor neurons. Upper motor neuron cell bodies are located within the cerebral cortex of the brain and brain stem centers including the vestibular nucleus and reticular formation. Lower motor neuron cell bodies are located in the ventral horn of the spinal cord and the cranial nerves of the brainstem. The axons from upper motor neurons typically project to interneurons in the spinal cord, although they can form direct synapses with lower motor neurons (Pocock & Richards, 2006). The axons from lower motor neurons typically project to muscle fibers, making them the link between the upper motor neurons in the brain and the muscles (Bear, Connors, & Paradiso, 2015; R. E. Burke, 2007).

1.1.2 The brain and its motor cortex

The brain is the most complex organ in the human body and serves as the center of the nervous system. The cerebral cortex is a region of the brain which is considered to be the largest site of neural integration in the central nervous system, containing approximately 14-16 billion neurons (Saladin, 2011). The motor cortex is the region of the cerebral cortex involved in the planning, control, and execution of voluntary movements (Tortora & Derrickson, 2014).

The motor cortex is further divided into three key areas: the primary motor cortex, the supplementary motor cortex, and the premotor cortex (Figure 2a). First, the motivation for

movement is developed. Signals are then transmitted through interneurons to the upper motor neurons of both the pre- and supplementary motor cortex, which together develop a motor plan. The motor plan is used to determine what muscles need to contract and to what degree. This motor plan is then transmitted to the primary motor cortex (M1), which is topographically organized by different cortical representations of muscles (Figure 2b). The size of these cortical representations corresponds with the degree of complexity in the movements that each muscle performs. For example, hand muscles have a large cortical representation and are capable of fine motor control (Graziano, Taylor, Moore, & Cooke, 2002). The upper motor neurons within these cortical regions then transmit signals down to the lower motor neurons in the spinal cord via descending motor pathways for execution of the movement.

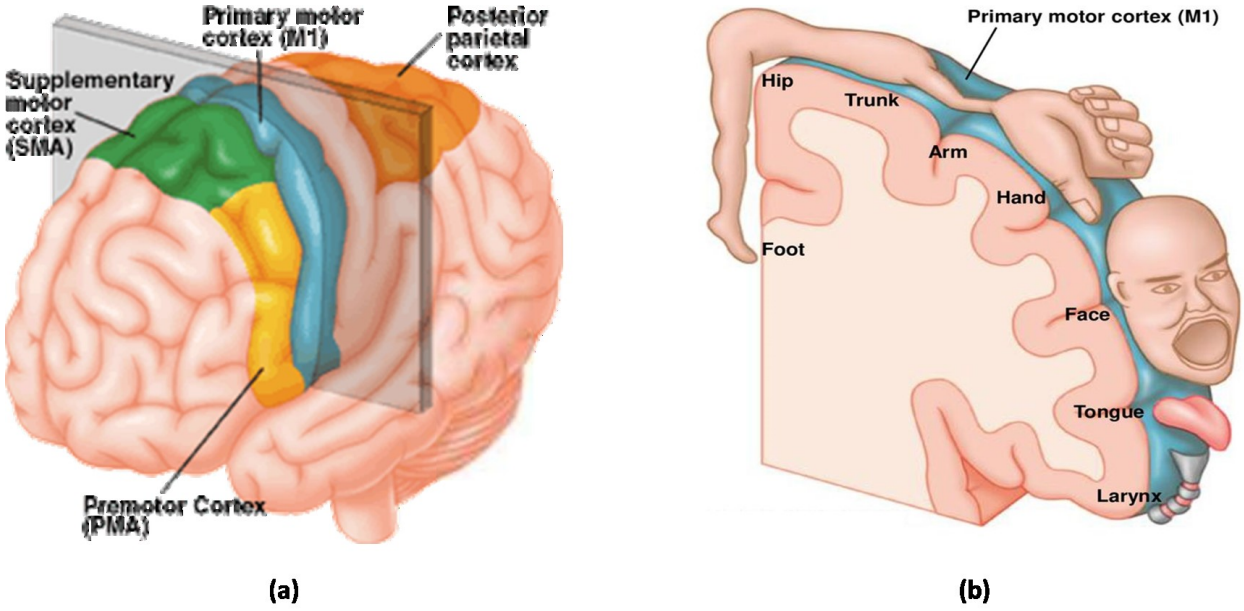

Figure 2. (a) Organization of the regions of the brain involved in planning and executing movements; (b) Topographical representation of the primary motor cortex (M1) (Jahangir et al., 2017)

1.1.3 The spinal cord

The spinal cord is an essential part of the CNS, as it allows for communication between the brain and the muscles through descending motor pathways and ascending sensory pathways. Descending pathways can be divided between the pyramidal tracts and the extrapyramidal tracts. The corticospinal tract, which is a part of the pyramidal tracts, consists of groups of axons which descend from the upper motor neurons and run longitudinally through the spinal cord and terminate on lower motor neurons within the spinal cord (Figure 3a) (Silva et al., 2014). Each lower motor neuron and the muscle fibers it innervates is known as a motor

unit. Depending on the nature of a muscle's motor activity, these motor neurons can innervate up to thousands of muscle fibers. Motor tracts and motor units are organized into spinal nerves, which project to innervate muscle at five vertebral levels (Figure 3b).

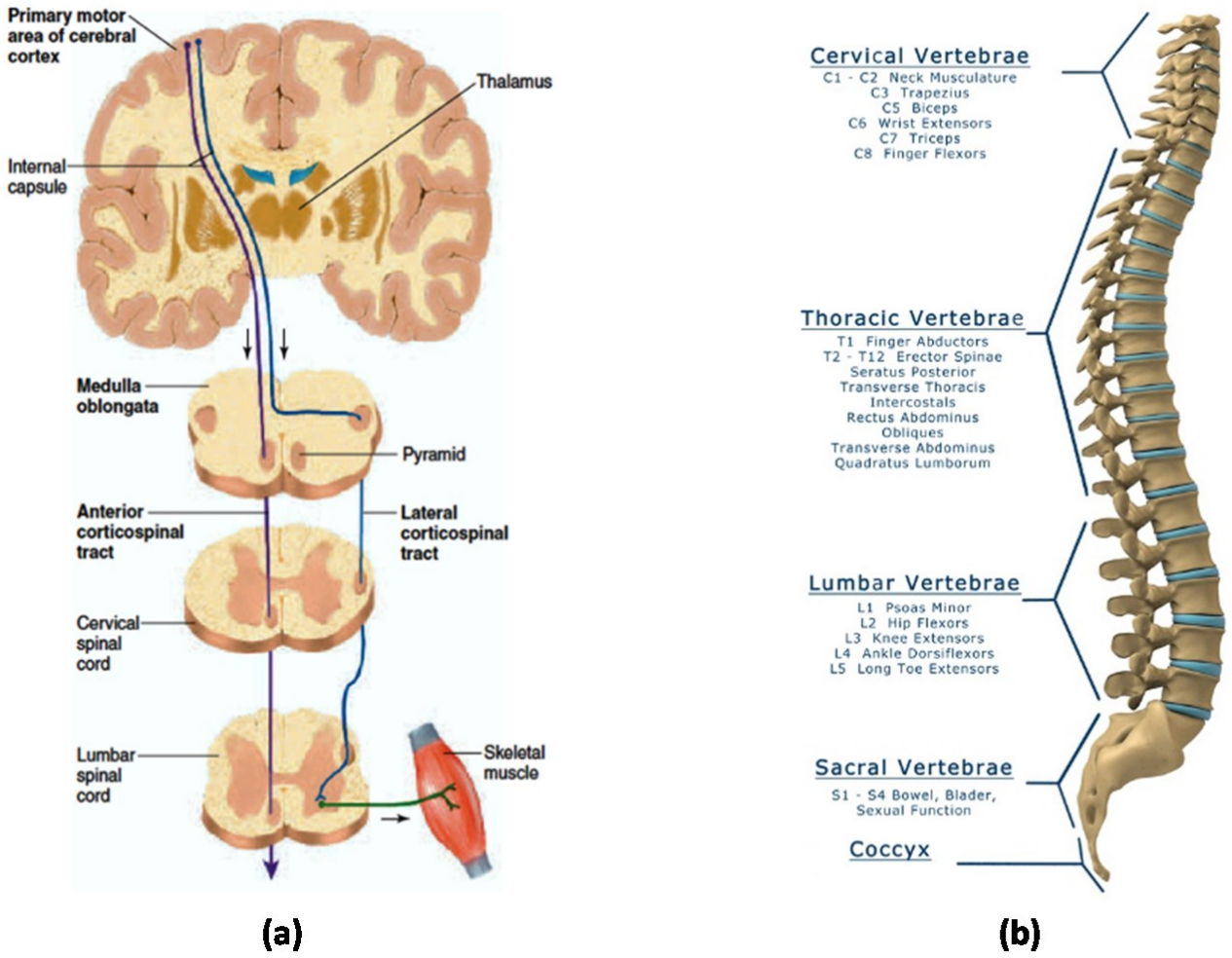

Figure 3. (a) Depiction of descending motor pathways; (b) Sections of the spinal cord labeled with the muscles innervated by the respective spinal nerves ("Moving Forward - Rehabilitation & Wellness Center," 2015; Silva et al., 2014)

1.1.4 Neuroplasticity

The CNS is not a static system, but rather an adaptable and modifiable system which undergoes dynamic plastic changes over the course of our lives (Cohen, Brasil-Neto, Pascual-Leone, & Hallett, 1993; Kaas, 1997). The ability for this system to respond to internal or external stimuli by reorganizing its structures, functions, and connections, is known as neuroplasticity (Cramer et al., 2011). Within the CNS, neuroplasticity is essential in the process

of learning new motor skills and recovery of function after an injury (S. J. Martin, Grimwood, & Morris, 2000; Alvaro Pascual-Leone, Amedi, Fregni, & Merabet, 2005).

Evidence suggests that plastic reorganization of the CNS is driven by the activity of neuron synapses and the circuits in which they operate (Klomjai, Katz, & Lackmy-Vallée, 2015; Triggs, 2004). An increases in synaptic activity is referred to as long-term potentiation (LTP), while a decrease in synaptic activity is referred to as long-term depression (LTD) (Bliss & Lomo, 1973). The mechanism behind LTP involves the NMDA receptor and excitatory neurotransmitters such as glutamate. An increased release of glutamate from the presynaptic neuron can open the NMDA receptors and allow for a large and fast influx of Ca^{2+} to the postsynaptic neurons. As this continues, Ca^{2+} will begin to accumulate in the postsynaptic neuron and thus increase its responsiveness for days or even weeks (i.e. long-term potentiation). While LTP is caused by a large and fast change in Ca^{2+} concentration, LTD results from a small and slow change in Ca^{2+} concentration.

1.2 Transcranial magnetic stimulation

One method of evaluating changes in the CNS that result from neuroplasticity is transcranial magnetic stimulation. Transcranial magnetic stimulation (TMS) is a form of non-invasive brain stimulation that is able to induce an electrical current in a specific location of the brain. This is done by passing several thousand amps of electrical current through a wire coil for a period of time (< 1 ms), which produces brief and rapidly changing magnetic fields. These magnetic fields penetrate the brain and generate an electrical current, as by Faraday's law of electromagnetic induction. If the electrical current in the brain causes depolarization of cortical neurons, an action potential is generated in neurons (P. M. Rossini et al., 2015).

The strength of the induced current can be altered by changing the pulse configuration of the current passed through the coil. The two main types of pulse configurations are monophasic and biphasic (Figure 4). The monophasic pulse provides stimulation through a strong initial increase in current, followed by a non-stimulating dampened reverse current. While the monophasic pulse has a single phase of stimulation, the biphasic pulse has two. The biphasic pulse consists of an initial increase in current, followed by a reversed current, and then additional increase in current. This causes two induced currents within the brain, the combination of which produces the net effect (Kammer, Beck, Thielscher, Laubis-Hermann, & Topka, 2001). This effect can be further varied depending on the direction of the induced

current within the brain (i.e. posterior-anterior or anterior-posterior), which can be altered via the stimulation parameters or coil positioning (Kammer et al., 2001).

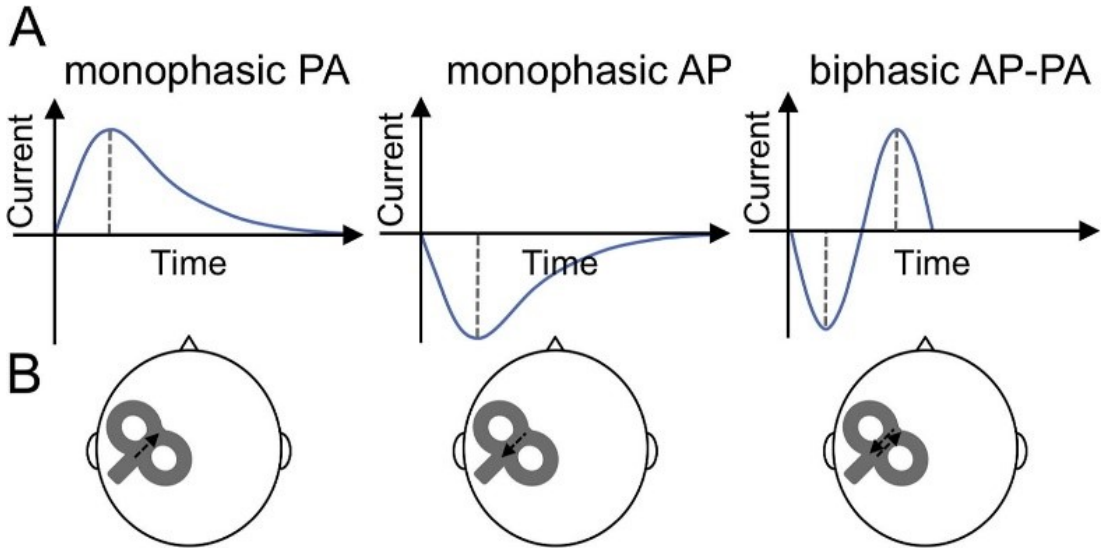

Figure 4. Diagram of TMS pulse waveforms and their induced current(s). **A)** Pulse waveforms for a monophasic pulse delivered in a posterior-to-anterior (PA) and anterior-to-posterior (AP) fashion, and a biphasic pulse. **B)** Depiction of the TMS coil positioned over the motor cortex with arrows showing the direction of the induced current(s) in the brain (Davila-Perez, Jannati, Fried, Cudeiro, & Pascual-Leone, 2018).

Along with pulse configuration, the focality of the TMS coil can also affect the strength and accuracy of the induced current (Thielscher & Kammer, 2004). Focality can be defined according to the half-field spread ($S_{1/2}$), which represents the area of the electric field's tangential spread across the cortex while accounting for the depth at which the electric field penetrates (Deng, Lisanby, & Peterchev, 2013). By changing the shape and size of the TMS coil (Figure 5), the focality and depth of stimulation can be modified (Figure 6) (Rastogi, Lee, Hadimani, & Jiles, 2017). While the method of use and target cortical region can influence the type of coil to be used, coils which increase focality are typically more desirable as they reduce the amount of runoff stimulus to non-targeted cortical areas. The traditional circular field coils had focalities in the range of 34 cm^2, however more recently developed coil designs such as the Figure-8 coil can have a focality as low as 5 cm^2 (Rastogi et al., 2017). This coil design in particular has played a major role in TMS studies which target the cortical representations of muscles in the primary motor cortex, as these cortical representations can be only a few square centimeters in size (ex. biceps = 16cm^2) (Brouwer & Hopkins-rosseel, 1997; Fassett, Turco, El-sayes, & Nelson, 2018).

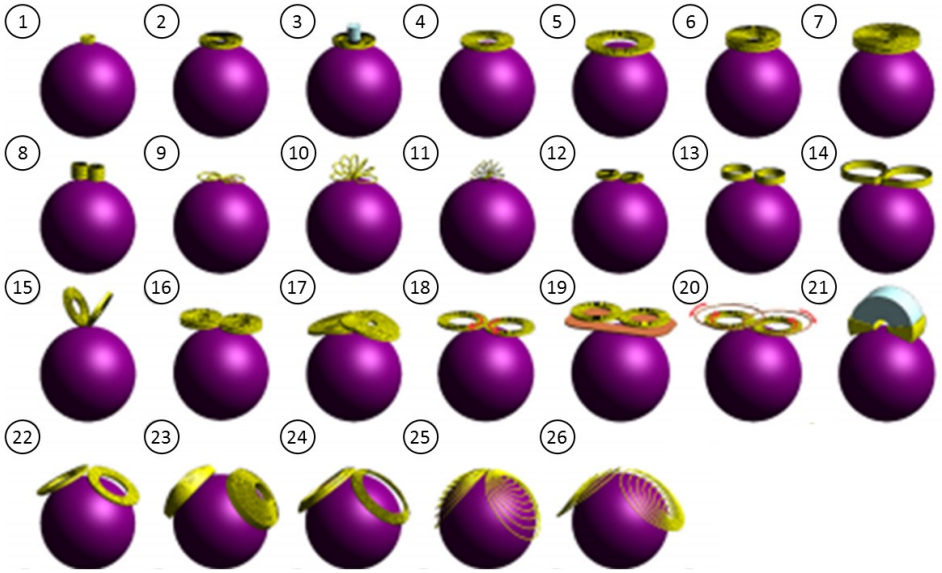

Figure 5. Simulation models of various TMS coil configurations: (1) Animal mini-coil, (2) Magstim 50 mm circular coil (P/N 9999), (3) 50 mm circular coil with iron core, (4) Magstim 70 mm circular coil (P/N 3192), (5) Magstim 90 mm circular coil (P/N 3192), (6) Magstim animal MST coil, (7) Magstim human MST coil (S/N MP39) (8) 3-layer double coil, (9) double butterfly, (10) circular slinky-7 coil, (11) rectangular slinky-7 coil, (12) Magstim 25 mm figure-8 (P/N 1165), (13) Cadwell Corticoil, (14) Cadwell B-shaped coil, (15) 50 mm V-coil, (16) MagVenture C-B65 butterfly coil, (17) MagVenture MC-B70 butterfly coil, (18) Magstim 70 mm figure-8 coil (P/N 9925, 3190), (19) 70 mm figure-8 with shielding plate, (20) 70 mm figure-8 with active shield (5 turns), (21) Neuronetics iron-core figure-8 coil (CRS 2100), (22) MagVenture D-B80 butterfly coil, (23) MagVenture MST twin coil, (24) Magstim double cone coil (P/N 9902), (25) eccentric double cone coil with center-dense windings, (26) eccentric double cone coil with center-sparse windings (Figure adapted from Rastogi et al., 2017).

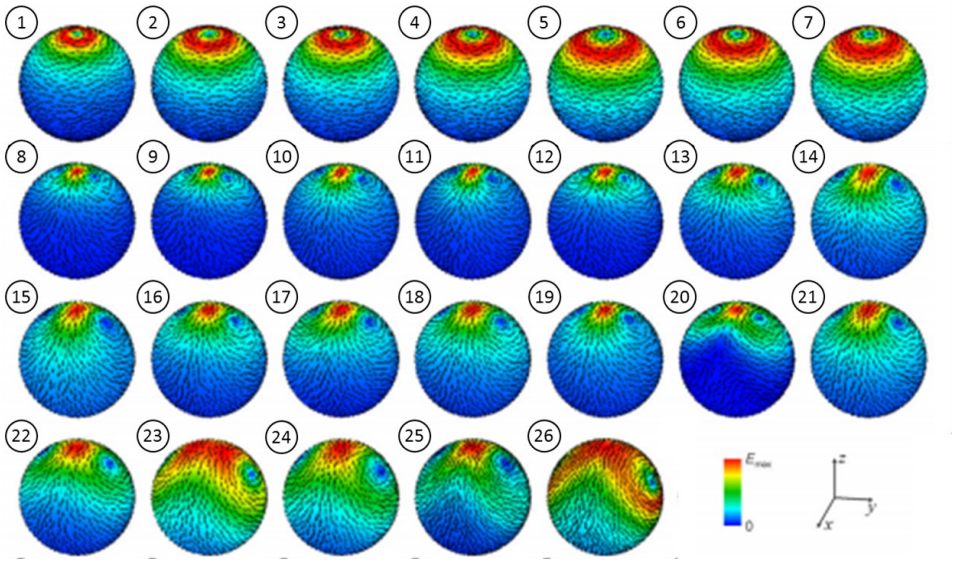

Figure 6. Induced electric field distribution on the brain surface by the TMS coils from Figure 5. Electric field magnitude is plotted via a color map normalized to the field maximum in the brain, for each coil. Arrows indicate the direction of the electric field (Figure adapted from Rastogi et al., 2017).

1.2.1 Measuring corticospinal excitability

When TMS is targeted to the cortical representation of a muscle within the motor cortex, the induced action potential will then travel down the pyramidal tract and through the spinal cord. Within the spinal cord, the electrical signal can be recorded through epidural electrodes as D-waves and I-waves. D-waves reflect the direct activation of axons which are activated by TMS, while I-waves come in later volleys as a result of indirect synaptic activation of the same pyramidal tract neurons (Klomjai et al., 2015; P. M. Rossini et al., 2015). The lower motor neurons in the spinal cord then recruit the respective muscle fibers to elicit a muscle response known as a motor evoked potential (MEP) on the contralateral side of the body (Figure 7). Using electromyography (EMG) sensors located on the muscle, the amplitude of MEPs can be recorded and used to evaluate changes in the excitability of the corticospinal motor pathway (corticomotor excitability) (Klomjai et al., 2015).

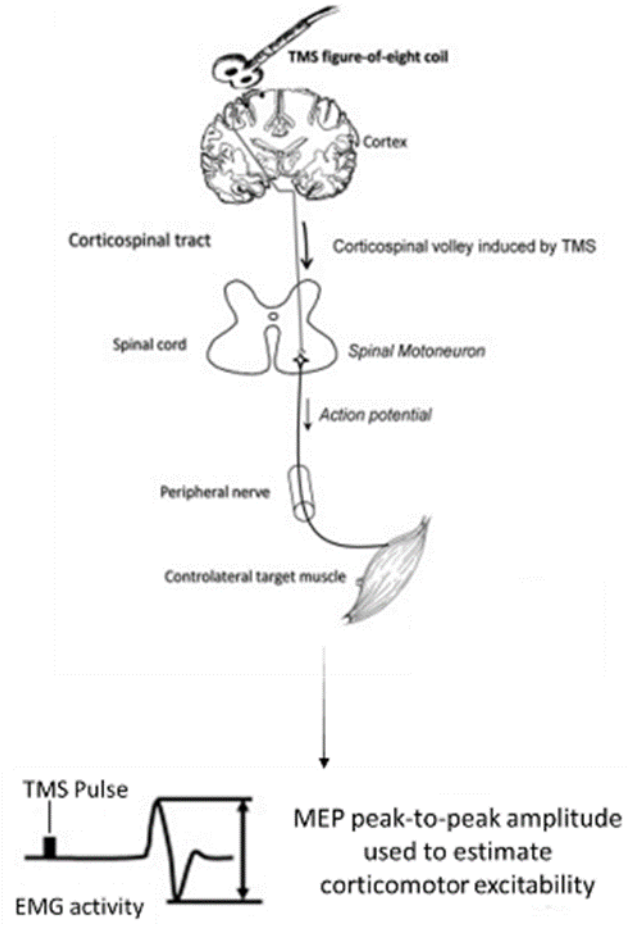

Figure 7. Transcranial magnetic stimulation (TMS) applied over the motor cortex activates neurons which evoke a descending volley of signals down the corticospinal tract. This then activates the motoneurons which causes the contralateral muscle to contract, thus evoking a motor-evoked potential (MEP) which can be used to evaluate corticomotor excitability (Klomjai et al., 2015).

The intensity of TMS used to elicit MEPs is determined based on the individual's cortical motor threshold. The motor threshold is defined as the minimal stimulation intensity required in order to elicit a non-random muscle response which produces a MEP of minimal amplitude (Boroojerdi, Battaglia, Muellbacher, & Cohen, 2001). The stimulation intensity required to elicit a non-random muscle response when the muscle is fully relaxed is known as the resting motor threshold (RMT). An active motor threshold (AMT) can also be determined when the muscle performs a slight tonic contraction, typically at 20% of maximal muscle strength (P. M. Rossini et al., 2015). While both of these thresholds can be used to evaluate the excitability of the cortical motor region in an individual, inherent changes to the excitability of the cortical and spinal neurons can cause some degree of uncertainty. Therefore, when determining motor thresholds, it is important to reduce technical variability as much as possible by maintaining coil position, motor state of the muscle, and environmental noise.

MEPs and motor thresholds serve as measures of corticospinal and motor cortical excitability respectively, and thus rely on different physiological mechanisms. MEPs are affected by both inhibitory and excitatory modulators within the neuronal networks, particularly those related to sodium-channel inactivation (U. Ziemann, Lönnecker, Steinhoff, & Paulus, 1996; Ulf Ziemann et al., 2015). Theories suggest that sodium-channel inactivation leads to a decrease in action potential firing, which in turn reduces synaptic transmissions and the excitability of I-waves (U. Ziemann et al., 1996). Motor thresholds on the other hand, are not affected by inhibitory modulators which affect GABA. They are only affected by modulators that block the voltage-gated sodium channels and affect the excitability of cortico-cortical axons and their contacts to corticospinal neurons. As a result of these differences, changes in MEP amplitude can occur without there being a significant change in the motor thresholds (Ulf Ziemann et al., 2015).

1.2.2 Measuring changes in neuroplasticity

Single pulse TMS is able to provide valuable metrics for evaluating changes that result from neuroplasticity. Stimulation of the motor cortex and recording MEPs allows for a cortical output map to be generated that can be correlated with measures of an individual's functional capacity (Alvaro Pascual-Leone et al., 1998). These can then be used to show reorganization of the CNS following injury or during the motor learning of a new skill.

Motor learning refers to the practice of repeating voluntary motor task(s) which results in improvements to motor performance (Iezzi et al., 2010). Motor learning typically occurs in phases (Table 1). In the early phases, motor performance starts out slow and variable, until it is gradually retained and consolidated over the course of several hours. In the late phases of motor learning, further incremental improvements can be attained through additional motor practice (Agostino et al., 2008; Iezzi et al., 2010; Teo, Swayne, Cheeran, Greenwood, & Rothwell, 2011). The early stages of motor learning are known to be mediated by neuroplastic processes within the motor cortex (Agostino et al., 2008; Iezzi et al., 2010; Rioult-Pedotti, Friedman, & Donoghue, 2000; Teo et al., 2011). Rioult-Pedotti et al. found that while learning a new motor skill, synaptic activity increased as a result of LTP effects within the motor cortex of rats (Rioult-Pedotti et al., 2000). These findings appear to hold true in humans as well and have been shown through functional neuroimaging studies performed during skill learning (Bischoff-Grethe, Goedert, Willingham, & Grafton, 2004; Jenkins, Brooks, Nixon, Frackowiak, & Passingham, 1994).

Table 1. Phases of motor learning and the learning attributes associated with each (Gadbury-Amyot, Purk, Williams, & Van Ness, 2014)

Stages of Motor Learning Associated with Motor Performance	Stages of Competence	Attributes
Cognitive (Trial and Error)	Novice	Requires explicit directions, small steps, standardized or ideal circumstances, slow, stiff or rigid, hesitant, extrinsic feedback, rules, dependence on faculty, isolated skills to provide foundation for later performance
↓	Beginner	Application of what has been learned, some judgment and recognition of need to adjust to rules, guided performance, shows some initiative, extrinsically rewarded, semiconscious
Associative (targeted)	Competent	Ready to begin independent practice, has a range of judgment and procedures, capacity to accurately self-assess, understand what they are doing, conscious
↓	Proficient	Flawless, fluid, easily modified, conforms to context, intrinsically rewarded, appropriate values are internalized
	Expert	Has internalized standards, is self-managed, performance is accurate and integrated, semiconscious (automatic), intrinsically rewarded
Autonomous		

Changes that occur as a result of the increase in synaptic activity associated with motor learning can be evaluated using TMS. One method of doing so involves mapping the cortical

representations of muscles before and after a motor learning exercise. Studies have shown that the cortical representation of muscles involved in motor learning tend to be enlarged following training (Kossut & Siucinska, 1998). An example of this can be seen in the study performed by Pascual-Leone et al., where they observed an increase in the cortical representation of muscles involved in a finger exercise relative to the untrained hand, following a 20-30 min rest period. This concept was further proven in additional studies which revealed enlarged cortical representations of regularly used muscles, such as those in athletes and braille readers (Pascual-leone et al., 1991; Tyč, Boyadjian, & Devanne, 2005).

The increase in synaptic activity that results from motor learning is not localized to just the brain, as it is present throughout the entire corticospinal system. This can similarly be measured by using TMS to evaluate the change in MEP amplitude. Muellbacher et al. demonstrated this concept by using TMS to measure the change in MEP amplitude of muscles following a pinch training exercise. An increase in task performance was associated with an increase in force and acceleration of movements, as well as an increase in MEP amplitudes, which then returned to baseline once proficiency was achieved. The change in MEP amplitude was only present within the muscles associated with the exercise and did not occurring in unrelated muscles (Muellbacher, Ziemann, Boroojerdi, Cohen, & Hallett, 2001).

1.2.3 Repetitive TMS (rTMS)

Unlike single pulse TMS, repetitive TMS (rTMS) is able to induce long lasting changes that persist beyond the time of stimulation (Klomjai et al., 2015; Suppa, Huang, Funke, Ridding, Cheeran, Di Lazzaro, Ziemann, Rothwell, et al., 2016). Biphasic stimulators are primarily used for delivering rTMS as they are able to overcome the recharging time required to deliver consistent stimulus outputs, which can be delivered consecutively at intervals as short as 10 ms (100 Hz) (Sommer et al., 2006). Much of the research which has investigated the effects of rTMS has targeted the motor cortex, as its effects on corticospinal excitability can be readily evaluated through measures such as MEPs. While there is a limited understanding of the physiological effects of rTMS, there is some evidence that the after-effects resemble LTP- and LTD-like mechanisms (Klomjai et al., 2015).

The effects of rTMS on the corticospinal excitability depend on stimulation parameters such as the stimulation frequency, and the length of the stimulation period (Simonetta-Moreau, 2014). The results from numerous studies suggest that high frequency (> 3 Hz) rTMS

stimulation induces excitatory LTP like changes, while low frequency (< 1 Hz) rTMS stimulation induces inhibitory LTD like changes (Fitzgerald, Fountain, & Daskalakis, 2006). Studies which implement high frequency rTMS typically consist of measuring the cortical excitability before and after repeated applications of brief high intensity (~150% RMT) stimulation trains. These studies have observed an increase in corticospinal excitability, as measured by an increase in MEP amplitude, that can outlast the application period (Peinemann et al., 2004). On the other hand, studies which implement low frequency rTMS often use a single train of stimulation that lasts for 10-20 min. These studies have typically shown low frequency rTMS to decrease corticospinal excitability, as shown by a decrease in MEP amplitude, although these results are less consistent than those which implement multiple trains of stimulation at higher intensities (Fitzgerald et al., 2006).

1.3 Theta burst stimulation (TBS)

The original rTMS protocols were fairly straightforward as they simply consisted of either low or high frequency stimulation. However, as time progressed and more advanced equipment became available, new rTMS protocols were developed that consisted of patterned stimulation in order to elicit the same long-lasting responses in a shorter time period. One of the most established methods of patterned rTMS is theta burst stimulation. Theta burst stimulation (TBS) is able to induce changes in cortical excitability by providing bursts of high frequency stimulation in short intervals. TBS consists of three TMS pulses of subthreshold intensity (~80% AMT) delivered at 50 Hz every 200 ms, putting the frequency of stimulation at 5 Hz, which is within the theta frequency range (4-7 Hz). The idea for TBS was originally derived from studies that examined the brains of rats, which found the hippocampus to discharge within the theta frequency range during exploratory behavior. TBS was able to induce plastic effects within these animal's brains and thus the protocols were adapted for humans (Suppa, Huang, Funke, Ridding, Cheeran, Di Lazzaro, Ziemann, Rothwell, et al., 2016).

Similar to rTMS, TBS can be delivered in different stimulation patterns to induce different effects in corticospinal excitability. In continuous TBS (cTBS), TBS is applied repeatedly for a period of time (20 – 40 seconds) without any pause. In intermittent TBS (iTBS), TBS is applied over the course of twenty ten-second trains, with each train consisting of TBS being delivered for 2 seconds, followed by an 8 second pause (Huang, Edwards,

Rounis, Bhatia, & Rothwell, 2005) (Figure 8). Compared to other forms of rTMS which need to be applied over a time period of 10-20 minutes, TBS protocols can be applied in a shorter time frame (2-3 min) making them more advantageous (Fitzgerald et al., 2006). Furthermore, because the stimulation intensity and number of pulses are relatively similar, the after-effects of TBS protocols appear to be more consistent than other rTMS methods (Hoogendam, Ramakers, & Di Lazzaro, 2010).

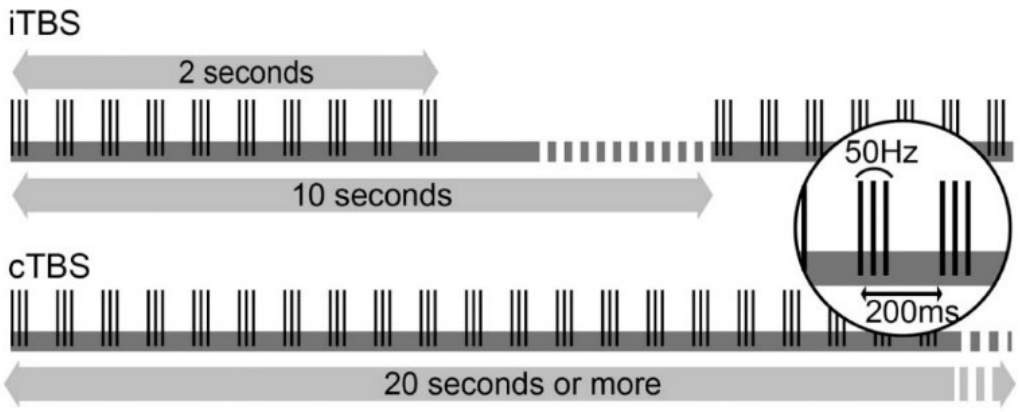

Figure 8. The stimulation patterns for both intermittent theta burst stimulation (iTBS) and continuous theta burst stimulation (cTBS) (Suppa, Huang, Funke, Ridding, Cheeran, Di Lazzaro, Ziemann, Rothwell, et al., 2016).

1.3.1 TBS in animals

The ability for TBS to induce plastic changes in the brain was originally studied in rats during exploratory behavior (Capocchi, Zampolini, & Larson, 1992; Diamond, Dunwiddie, & Rose, 1988; Larson & Lynch, 1986, 1989). However, the study of these effects faced a scaling problem as the brains of rats are roughly 700x smaller than the brains of humans, making focal stimulation of the motor region of the brain incredibly difficult. Even coils designed for rodents could not solve this problem completely, as the current flow required for stimulation would lead to overheating. Thus, the patterned stimulation of TBS was delivered using conductive electrodes applied directly to the area of interest. This allowed for enhanced focality and eliminated the limitations of using TMS coils (Barry et al., 2014; Hsieh et al., 2015).

The initial studies of TBS in anaesthetized rats were found to decrease the amount of the calcium-binding proteins parvalbumin and calbindin, which are expressed in GABAergic interneurons; these changes were found to last for hours or even days (Aydin-Abidin, Trippe, Funke, Eysel, & Benali, 2008; Benali et al., 2011). Changes in the amount of these proteins induce changes in the intracellular Ca^{2+} concentrations of the neurons, which lead to LTP/LTD

mediated changes, respectively, in neuronal plasticity (Grehl et al., 2015). It was found that iTBS reduced the expression of parvalbumin, which regulates inhibition in interneurons, while cTBS was found to reduce the expression of calbindin, which controls the output of interneurons (Benali et al., 2011). These findings suggest that the different TBS protocols have different effects on the cortical network and served as the foundation for understanding the effects of TBS in humans.

1.3.2 TBS in humans

Similar to the mechanisms of function in animal studies, the effect of TBS in humans depend on LTP- and LTD-like changes that are mediated by the intracellular Ca^{2+} concentrations of the neurons. Our understanding of the mechanisms behind TBS in humans can be explained using a three-stage model based on a simplified version of post-synaptic plasticity (Huang, Rothwell, Chen, Lu, & Chuang, 2011). TBS begins by triggering a Ca^{2+} influx to the postsynaptic neurons, the rate and degree of which causes changes to the synaptic strength. This results in a combination of LTP and LTD effects which determine the after-effects of TBS. The combination of these LTP and LTD effects can be altered based on the type of TBS used. Studies have shown that LTP effects are reduced when the number of applied bursts and number of trains are increased (Abraham & Huggett, 1997; Larson & Lynch, 1986). Furthermore, while a train of stimulation can have an initial facilitatory effect, longer trains actually cause an inhibitory effect (Beierlein, Gibson, & Connors, 2003). This mechanistic understanding of TBS provides support for the observed effects of cTBS and iTBS on corticomotor excitability, which have been found across numerous studies; Being that cTBS, which uses long trains of theta bursts, decreases MEP amplitudes, while iTBS, which uses short trains of 10 bursts, increases MEP amplitudes (Huang et al., 2005; Klomjai et al., 2015; Suppa, Huang, Funke, Ridding, Cheeran, Di Lazzaro, Ziemann, Rothwell, et al., 2016).

While the aforementioned effects have been found in numerous studies, the response to TBS still remains highly variable both across and within individuals. As a result, some studies have found a lack of significant findings when analyzing their group data (P. G. Martin, Gandevia, & Taylor, 2006; Perellón-Alfonso et al., 2018). There are several factors which could contribute to this inter- and intra-variability, such as genetics, the state of circulating hormones, and previous levels of activity (Cheeran et al., 2008; M. C. Ridding & Ziemann, 2010). However, the differences in the intracortical networks activated by TMS could be the prevailing

cause of this variability (Hamada, Murase, Hasan, Balaratnam, & Rothwell, 2013). Hamada et al. showed that individuals in which late I-wave circuits are readily activated by TMS are more likely to respond in the expected fashion for both cTBS and iTBS. This difference among individuals accounted for nearly 50% of the variability that was observed in the response to TBS. This suggests that some individuals may be more apt to respond to TBS than others, which is why some studies have gone as far as to categorize individuals as either “responders” or “non-responders” (Hinder et al., 2014; Nettekoven et al., 2015; Perellón-Alfonso et al., 2018). Despite these factors of variability, comprehensive reviews have shown that across studies, the respective effects of iTBS and cTBS on corticomotor excitability hold true (Chung, Hill, Rogasch, Hoy, & Fitzgerald, 2016a; Lowe, Manocchio, Safati, & Hall, 2018). Thus, further studies are needed to determine the physiological mechanisms that underlay the effectiveness of TBS protocols and populations that would most benefit from their effects.

1.3.3 Improving motor function with iTBS

Of the different forms of TBS, iTBS shows the most potential for improving motor function and aiding in the motor learning process. The rationale is that the ability for iTBS to induce LTP-like effects in the motor region of the brain can cause an increase in corticomotor excitability, which is associated with motor learning and skill acquisition. Therefore, iTBS could be implemented during the early phases of motor learning to aid in that process, or in the later phases to improve the performance of existing muscle function. This has previously been demonstrated in rats, as iTBS was able to improve their ability to perform a tactile discrimination task while in the dark (Mix, Benali, Eysel, & Funke, 2010). There have even been a few studies in humans to demonstrate this ability, with one study showing iTBS to enhance the learning of finger movements in humans when given 10 minutes beforehand (Agostino et al., 2008; Teo et al., 2011). However, the effect of iTBS on the corticomotor excitability of individual muscles remains highly variable across studies and needs to be further understood.

The majority of studies examining the effects of iTBS on corticomotor excitability in humans have targeted the distal muscles of the upper limb in non-impaired individuals, particularly the first dorsal interosseous (FDI). This is likely because the FDI is an easier target than more proximal muscles, such as the biceps brachii, as distal muscles have a higher density of corticospinal neurons projecting to the muscle and represent larger motor map areas

that are more accessible to iTBS (Bawa, Hamm, Dhillon, & Gross, 2004; Malcolm et al., 2006). These studies have found that iTBS can increase the amplitude of MEPs in non-impaired individuals for up to 30 minutes (Hinder et al., 2014; Huang et al., 2005). However, there appears to be a high degree of variability in the iTBS induced after-effects within and across individuals (Hamada et al., 2013; López-Alonso, Cheeran, Río-Rodríguez, & Fernández-Del-Olmo, 2014; Vernet et al., 2014a). Not every individual has been shown to exhibit the excitability changes associated with iTBS, with some individuals even showing different responses across multiple sessions (Hinder et al., 2014; Perellón-Alfonso et al., 2018). This variability can also be seen in studies which implement a sham iTBS control, resulting in no significant differences between the active and sham stimulations (Perellón-Alfonso et al., 2018).

While further research targeting the FDI is warranted due to variability in the observed after-effects, other muscle groups may be appropriate targets for iTBS. More proximal muscles may respond differently to iTBS due to differences in corticospinal control (Neige, Massé-Alarie, Gagné, Bouyer, & Mercier, 2017). One study which investigated the effects of iTBS targeting the flexor carpi radialis (FCR) found that iTBS increased the corticomotor excitability of the muscle in non-impaired individuals. This study also found that the difference between the RMT of the FCR and its antagonist muscle correlated with the efficacy of iTBS (Mirdamadi, Suzuki, & Meehan, 2015). Using RMT of the target muscle as a predictive method for determining the efficacy of iTBS could be a powerful tool for understanding the variability of after-effects associated with iTBS. However, further research is needed to determine if this correlation holds true in other muscles.

Chapter 2: Overview of spinal cord injury

Spinal cord injury (SCI) is a debilitating medical condition that has a life-long impact on the individual. Damage to any of the spinal nerves can cause a disruption in the signaling pathways of the lower motor neurons, thus affecting the degree of sensory and motor function in the muscles below the site of injury. When the spinal cord is completely compressed or severed (complete SCI), the lower motor neurons below the site of injury are unable to transmit or receive signals, resulting in total loss of sensory and motor function in their respective muscles. If the spinal cord is only partially compressed or damaged (incomplete SCI), some signals from the upper motor neurons are still able to be transmitted beyond the site of injury (Silva et al., 2014). As a result, the remaining pathways within the central nervous system after incomplete SCI are able to reorganize themselves in an effort to preserve some function of the muscles (A. Curt, Schwab, & Dietz, 2004; Ditunno, Burns, & Marino, 2005; B. Dobkin et al., 2007).

There are currently an estimated 288,000 individuals living with spinal cord injury in the United States, with an additional 17,700 new cases occurring each year (*Facts and Figures at a Glance*, 2018). Of all these cases, the most common form is incomplete tetraplegia (Figure 9). Incomplete tetraplegia can be caused by damage to the low cervical section of the spinal cord (C5-C8), resulting in the individual having deficits in their upper limb function. Upper limb function is critical for performing daily activities and is often rated as the most desired ability to be regained by individuals with tetraplegia in order to improve their quality of life (Anderson, Fridén, & Lieber, 2009). Therefore, methods of providing motor re-education to these muscles after injury is crucial in order to maintain and improve their function.

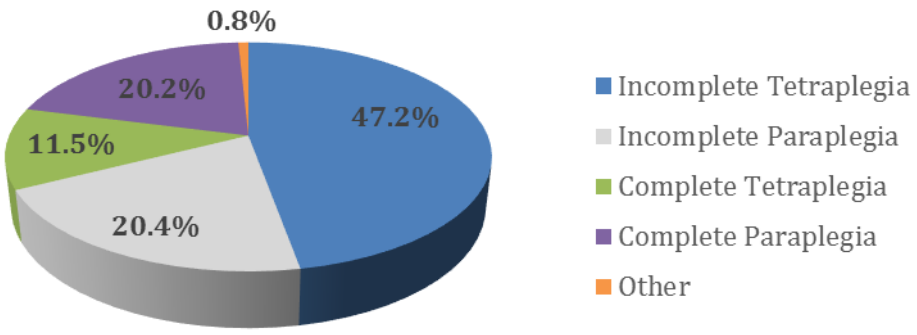

Figure 9. Statistics of the most common neurological categories following spinal cord injury. (National Spinal Cord Injury Statistical Center, 2018)

2.1 Assessing impairment (ASIA scores)

In order to properly understand the potential for functional recovery after SCI, accurate and reliable tests which can evaluate motor and sensory function are essential (Silva et al., 2014). These tests can be assessed based on a variety of data: endpoint measures, which are assessed based on some goal to be reached; kinematic measures, which can be assessed from qualitative descriptions of movement to continuous quantitative measurements; and kinetic measures, which are assessed through quantifiable metrics such as grip strength (Muir & Webb, 2000). Tests such as these are frequently used in the American Spinal Injury Association (ASIA) assessment protocol. The ASIA assessment uses two sensory examinations and a motor examination in order to quantify the severity of the SCI, and then classifies the individual according to an impairment scale (Table 2).

Table 2. American Spinal Injury Association Impairment Scale (Roberts, Leonard, & Cepela, 2017)

A	Complete	No motor or sensory function is preserved in the sacral segments S4–S5
B	Incomplete	Sensory function preserved but not motor function is preserved below the neurological level and includes the sacral segments S4–S5
C	Incomplete	Motor function is preserved below the neurological level, and more than half of key muscles below the neurological level have a muscle grade less than 3
D	Incomplete	Motor function is preserved below the neurological level, and at least half of key muscles below the neurological level have a muscle grade of 3 or more
E	Normal	Motor and sensory function are normal

2.2 Recovery after SCI

For individuals with tetraplegia, the complete or partial loss of sensory and motor function in their limbs can leave them heavily reliant on attendants to aid them in performing daily activities. With upper limb motor function being one of the core determinants for performing these daily activities, it is frequently the number one desired ability to be regained after injury (Anderson et al., 2009). Fortunately, there are methods which are able to help enhance upper limb motor function in those with tetraplegia.

2.2.1 Upper limb rehabilitation

The recovery of motor function in impaired muscles after SCI depends greatly on the level and types of motor training performed (Edgerton et al., 2001; Wernig, Muller, Nanassy, & Cago, 1995). Therefore, extensive strength training and aerobic conditioning are necessary to give individuals with tetraplegia the physical capacity to perform daily activities (B. H. Dobkin, 2007). Fortunately, the principles for strength training used in non-impaired individuals can also be used in those with tetraplegia. Resistance training is the main method used to strengthen impaired muscles and involves moving the muscles against some resistance during concentric or eccentric muscle contractions (B. H. Dobkin, 2014). For this type of training, the primary muscle targets are those related to the flexion and extension of the wrists and elbows, as well as grip strength. These are core muscle that aid in performing daily activities and are frequently impaired in individuals with tetraplegia. Tolerance for using these muscles can be further enhanced with aerobic conditioning, which can be achieved by exercising the upper extremities through the use of arm ergometry (B. H. Dobkin, 2014). Regular aerobic conditioning can not only improve tolerance of motor function during daily activities, it can also reduce the rate of decline in individuals as they age with their injury (B. H. Dobkin, 2014).

While these rehabilitation methods are capable of improving the performance of the remaining functional muscles, they are unable to restore muscle functions that were lost due to injury. However, a tendon transfer is a surgical approach which is able to partially restore these lost muscle functions (Figure 10). A tendon transfer involves transferring a tendon from a functional muscle that has a redundant function and reassigning it to perform a muscle function that was lost due to SCI (Fridén & Gohritz, 2012). For example, if the individual has lost function of their triceps brachii, the aim of the surgery is to restore elbow extension. Therefore, either the biceps brachii or brachioradialis, which can both be used elbow flexion, has its tendinous insertion relocated to perform elbow extension. Tendon transfer surgeries can also be used to restore voluntary thumb pinch, improve grip strength, and restore extension of the wrists (Freehafer, 1998; Johnstone, Jordan, & Buntine, 1988). However, the tendon transfer alone is not enough. The donor muscle must undergo extensive motor re-education and strength training for optimal outcomes to be achieved (Becker, Sadowsky, & Mcdonald, 2003).

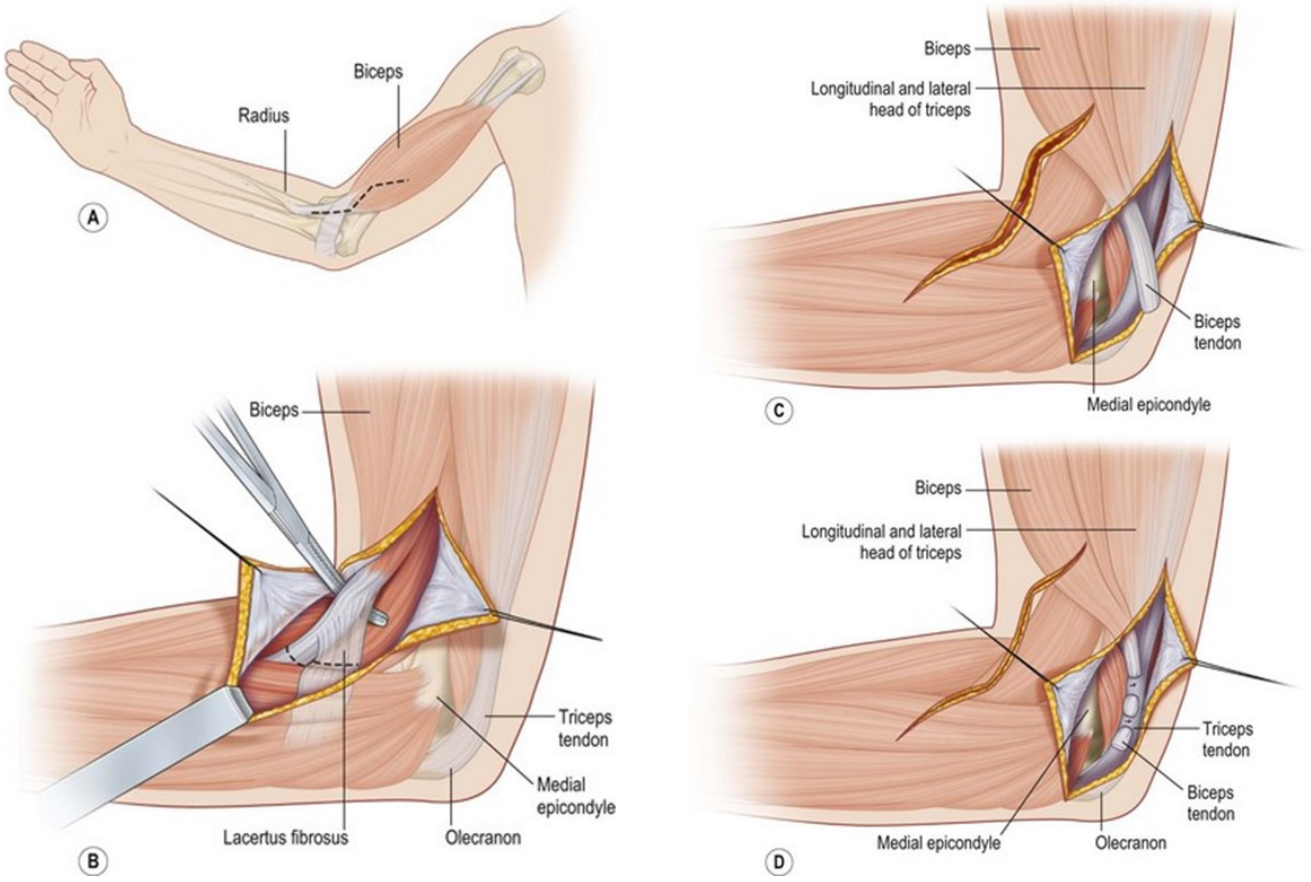

Figure 10. Depiction of the process for a biceps to triceps transfer to restore elbow extension function (Curtin & Hentz, 2016).

2.2.2 Neuroplastic changes

After a cortical lesion or spinal cord injury, the CNS is capable of undergoing plastic changes in an effort to preserve its functionality. The remaining functional neuronal structures can undergo reorganization and change their activation patterns in order to preserve sensory and motor function (Cramer et al., 2011; Alvaro Pascual-Leone et al., 2005). These changes in neuroplasticity have been found to occur in both animals and humans which have experienced both central and peripheral injuries. One study which investigated neuroplasticity in monkeys with long-standing amputations found that the cortical areas controlling remaining functional muscles tended to be enlarged and even invaded cortical areas which controlled muscles lost due to injury (Qi, Stepniewska, & Kaas, 2000). This type of cortex reorganization has also been found to occur in humans with spinal cord injury (Bruehlmeier et al., 1998; Levy, Amassian, Traad, & Cadwell, 1990; Topka, Cohen, Cole, & Hallett, 1991). However, cortical areas are not the only regions subject to plastic change after injury. In mice which experienced

an incomplete SCI, it has been found that neurons in subcortical structures, such as the brainstem, are capable of axonal sprouting and forming new connections in order to reactivate forelimb representations in the somatosensory cortex (Jain, Catania, & Kaas, 1997).

The biological mechanisms which mediate this change in plasticity are still being investigated, however there is one that provides some strong evidence. It is theorized that changes in cortical plasticity are mediated by the removal of GABAergic inhibition in excitatory synapses. This could be due to the fact that GABA is the most influential inhibitory neurotransmitter in the brain, as 25-30% of the neuronal population in the motor cortex is comprised of GABAergic neurons (Jones, 1993). Studies such as one performed by Hendry and Jones have provided support for this theory by showing that changes in GABAergic inhibition significantly impact cortical plasticity (Hendry & Jones, 1986). It has also been found that intracortical GABAergic inhibition is reduced in individuals with SCI (Roy, Zewdie, & Gorassini, 2011). Thus, cortical reorganization after SCI could reduce GABAergic inhibition in an effort to help promote plastic changes to preserve motor function.

While the CNS is able to undergo plastic changes in an effort to preserve function after injury, not all changes are beneficial. Maladaptive changes in plasticity can lead to negative symptoms such as pain, spasticity, and autonomic dysreflexia (Christensen & Hulsebosch, 1997). Spasticity can be characterized by painful muscle spasms in response to stretch or noxious cutaneous stimulation, while autonomic dysreflexia is characterized by a sudden increase in blood pressure (Rabchevsky, 2006; Rabchevsky & Kitzman, 2011). These negative symptoms are thought to be caused by sprouting of neurons below the site of injury, which is correlated with an increase in the input to interneurons, however further research investigating these complications is still needed (Krenz & Weaver, 1998). Each of these negative symptoms can impact an individual's ability to perform daily activities, therefore it is important to look for methods which can help guide these plastic effects in order to optimize the functional outcomes after SCI.

2.3 Inducing neuroplastic changes with rTMS after SCI

With the majority of spinal cord injuries being incomplete, there is an opportunity to help facilitate neuroplastic changes which can improve motor function below the site of injury. These neuroplastic changes can consist of the neural repair and regrowth of connections across the site of injury through axonal sprouting, as well as increasing the excitability of the

remaining connections. rTMS provides a method to achieve these neuroplastic changes through its ability to induce LTP- and LTD-like effects throughout the CNS, including the targeted motor region, corticospinal tract, and neuronal circuits (Berardelli et al., 1998; Perez, Lungholt, & Nielsen, 2005; Valero-Cabré, Oliveri, Gangitano, & Pascual-Leone, 2001).

2.3.1 Promoting neuroregeneration and neural repair with rTMS

After SCI, axonal sprouting provides an opportunity to restore connections across the site of injury to help restore function. This regenerative sprouting can occur spontaneously after SCI but is often temporary and subsides after a few weeks (Von Meyenburg, Brösamle, Metz, & Schwab, 1998). The diminution of axonal sprouting is thought to be the result of local production of inhibitory proteins that prevent axonal outgrowth (Schwab & Caroni, 1988). The repeated stimulation from rTMS promotes an accumulation effect of metabolism and growth that can overcome this phenomenon and induce neuroregeneration (Yang, Liu, Xie, Liu, & Tian, 2015). An example of this method can be seen in the animal experiment performed by Anne-Lise et al. Their study showed that 10 Hz rTMS delivered over an 8-week period improved the motor function of the hindlimbs in SCI rats with T10-11 injuries. This improved motor function was also found to be associated with an increased density of descending nerve fibers in the posterior segment of the damaged spinal cord (Poirrier et al., 2004). Despite these promising findings, the main limitation of this stimulation approach is the prolonged stimulation over the course of several days/weeks. This long period of stimulation is not practical for a therapeutic approach, especially since long stimulation periods can lead to inhibited neuronal excitability, as previously discussed (Song, Amer, Ryan, & Martin, 2015). Fortunately, iTBS has been shown to induce similar effects of neural repair and improved transmission after only two weeks of stimulation (Ljubisavljevic et al., 2015).

While rTMS is able to promote nerve regeneration, methods for nerve circuit stimulation should not be limited to just cortical stimulation. Local magnetic stimulation has also been shown to improve axonal regeneration and promote the recovery of nerve function in animal studies (Kolosova, Akoev, Ryabchikova, & Avelev, 1998). Therefore, co-activation of both the M1 region and spinal target of the corticospinal tract could promote effective neural circuit reconstruction better than either stimulation alone (Song et al., 2015). This theory has been demonstrated in the study performed by Song, et al., which targeted iTBS to the M1 region of SCI rats while co-activating the cervical spinal cord with trans-spinal direct current stimulation.

Their results showed that the combined stimulation facilitated forelimb MEPs in a greater fashion than either stimulation method alone and resulted in a 5.4 increase in axon length compared to the control group after 10 days of stimulation (Song et al., 2015). While this study shows the potential for the use of iTBS to induce axonal sprouting after SCI, stimulation protocols still need to be further optimized and investigated in conjunction with rehabilitation protocols before this method can be implemented as a form of rehabilitation.

Both rTMS and co-activation protocols show promise for improving motor function through the promotion of neuroregeneration. However, the effects of these protocols on the microenvironment which promotes neuroregeneration in humans needs further investigation (Zheng, Mao, Yuan, Xu, & Cheng, 2019). There are several studies which have investigated the ability of electromagnetic fields and electrical currents to promote axonal growth and differentiation of stem cells into neural-like cells (Zhu et al., 2019). More recent studies have begun using human based stem cell lines and shown these stimulation methods to help guide and enhance neural stem cell migration and differentiation (Choi et al., 2014; Du et al., 2018; Feng et al., 2012; Lee et al., 2018). These studies provide promising results and a rationale for continued research in neuroregeneration so that these rTMS and co-activation protocols can eventually be translated to clinical applications.

2.3.2 Effects of rTMS in humans with SCI

The application of rTMS to the motor cortex in non-impaired individuals has been shown to induce changes in excitability to the corticospinal motor system. High-frequency rTMS (≥5 Hz) typically increases the excitability of the system, while low-frequency rTMS (≤1 Hz) decreases it (M. C. Ridding & Ziemann, 2010). With these changes in excitability being linked to changes in motor function, rTMS provides a viable method to increase the excitability of the remaining functional corticospinal motor tracts in individuals with incomplete SCI and improve their motor function. However, there have been a limited number of studies which have investigated the effects of rTMS methods in those with SCI (Tazoe & Perez, 2015).

Based on the understanding that high frequency rTMS typically increases the excitability of the CNS, it has been the primary method used in studies. One study by Belci et al. delivered rTMS at 10Hz to the thenar muscle representation of the M1 region in 4 patients with incomplete SCI. Individuals participated in 5 days of sham rTMS, followed by 5 days of real rTMS. Real rTMS was found to improve the sensory and motor function of the muscle, as

assessed by the ASIA Impairment Scale and the mean time required to complete a 9-hole peg test. These improvements endured for at least 3 weeks in each participant. However, not all studies have found positive findings. Another study performed by Kuppuswamy et al. delivered rTMS at 5Hz to the muscle representation of the M1 region which had the lowest RMT value. This was performed in 15 individuals who had either complete or incomplete SCI, with each individual participating in 5 days of sham rTMS, followed by 5 days of real rTMS. It was found that rTMS did not induce any changes in sensory or motor function when evaluated by the ASIA impairment scale or most neurophysiological assessments, such as RMT or MEP amplitude. The only changes found occurred in the AMT of the first dorsal interosseous (FDI) muscle, which increased from baseline at 72 and 120 hours post real rTMS.

Ultimately, it is difficult to compare the variable results across these studies as there are often differences in several factors, including the targeted M1 region, stimulation parameters, method of measuring outcomes, and even the participants themselves. However, this high degree in variability is also present in the rTMS studies of non-impaired individuals. While the effects of rTMS may depend on the intensity of stimulation used, individual differences in cortical and subcortical neuronal organization must further contribute to these variable findings. This variability can be further affected by the plastic changes in neuronal organization that occur after SCI. Therefore, additional studies which investigate the effects of rTMS after SCI are needed to understand its effects on the corticospinal system.

2.3.3 Improving motor outcomes in humans with iTBS

Due to the consistency of its stimulation parameters, iTBS may be the most promising method of rTMS to help improve motor outcomes after SCI. Comprehensively, studies have found iTBS to increase corticomotor excitability, as measured by MEPs, in non-impaired individuals. However, due to the plastic changes in the CNS that occur after injury, the observed effects of iTBS in a non-impaired population cannot necessarily be translated to those with SCI.

Among the limited number of rTMS studies performed in individuals with SCI, there are few which have evaluated the ability for iTBS to modulate corticomotor excitability. The study by Fassett et al. is an example of such, as they investigated the effect of iTBS on the corticomotor excitability of the FCR muscle in individuals with incomplete cervical spinal cord injury. Their results ultimately showed that iTBS reduced the amplitude of MEPs recorded from

the FCR in the majority of instances (Fassett et al., 2017). While this does not reflect the increase in excitability that has been found in the non-impaired population, this study did demonstrate that corticomotor excitability is modifiable in individuals with incomplete SCI. However, further investigations are still needed in order to develop a better physiological understanding of these findings.

Chapter 3: Objectives and methods

3.1 Objectives of the study

Noninvasive neuromodulation techniques, such as iTBS, provide an opportunity to increase an individual's corticomotor excitability. This priming of the corticospinal system could further enhance the motor learning achieved with physical therapy and help improve functional outcomes in those with motor impairments, such as SCI. However, a broader understanding of the efficacy of iTBS to increase corticomotor excitability is needed to inform the design of combinatorial therapies that aim to improve motor function.

While the effects of iTBS have been evaluated in numerous studies with non-impaired individuals, they have not been studied as extensively in those with SCI. Damage to the corticospinal tract could greatly impact the effects of iTBS, thus affecting the potential for the observed effects seen in non-impaired individuals to be translated to those with SCI. More studies which investigate the effect of iTBS in those SCI are needed in order to understand its unique effect in this population of individuals and how they relate to the effects observed in non-impaired individuals.

With the majority of iTBS studies targeting distal muscles of the upper limb, such as the FDI, there is also a need to investigate its effects on other muscles. For those who have suffered from a lower cervical SCI, the distal muscles of the upper limb are likely to be more impaired than the more proximal muscles such as the biceps brachii. These proximal muscles are more suitable to undergo rehabilitation to improve their strength and function in performing daily activities, and can also be used surgically to restore muscle functions that were lost due to injury. This makes the more proximal muscles of the upper limb more functionally relevant targets for increases in corticomotor excitability in those with low cervical SCI.

The objectives of the following study were as follows. First, we sought to determine the effect of iTBS on the corticomotor excitability of the biceps brachii in nonimpaired individuals. With evidence showing that the effect of iTBS may depend on the difference in motor thresholds between the targeted muscles and its antagonist, we also sought to evaluate the correlation between the effects of iTBS and the difference between the RMT of the biceps and triceps. Next, we sought to determine the effect of iTBS on the corticomotor excitability of the biceps brachii in individuals with low cervical spinal cord injury. The correlation between the

effects of iTBS and the difference between the RMT of the biceps and triceps would similarly be evaluated.

3.2 Methods

3.2.1 Participants

Of the sixteen non-impaired individuals who were recruited for this study, ten of them completed all three sessions of the protocol (5 men, 5 women, average age 25.3 ± 5.6 years). Individuals with active motor thresholds (AMT) greater than 71% of maximum stimulator output (MSO) were excluded. This criterion was needed to ensure iTBS could be delivered at 80% of AMT since the intensity of the stimulator was limited to a maximum of 57% MSO. Testing was stopped on one individual due to an inability to consistently elicit MEPs ≥ 50 μV, and another individual who expressed discomfort during single pulse TMS.

In our spinal cord injury group, seven individuals completed all three sessions of the protocol (6 male, 1 female, average age 35.71 ± 13.0 years). Inclusion criteria required participants to be between the ages of 18 and 65 years old, have an injury to the lower cervical spinal cord at least one year prior to the date of participation, and have motor function classified according to the American Spinal Injury Association International Standards for Neurological Classification of Spinal Cord Injury at levels ranging from C5-C8. Exclusion criteria included presence of concurrent severe medical illness, including unhealed decubiti, use of baclofen pumps, existing infection, cardiovascular disease, significant osteoporosis, or a history of pulmonary complications.

All participants were screened to ensure safety of the TMS protocols and provided informed consent. The protocol was approved by the Institutional Review Board of Virginia Commonwealth University.

3.2.2 Experimental protocol

The protocol consisted of participants completing three sessions, with each session separated by a minimum of three days to prevent the potential for carry over effects. To control for variability that may result from diurnal effects, iTBS sessions were scheduled for early afternoons. In each session, participants were seated in a chair with their dominant arm at rest, the elbow in 90° flexion, and the forearm supinated (Figure 11). During portions of the protocol

involving TMS, participants wore a neck brace to minimize head movements and improve coil positioning. EMG signals were recorded with Spike 2 software (Cambridge Electronic Design, Cambridge, UK).

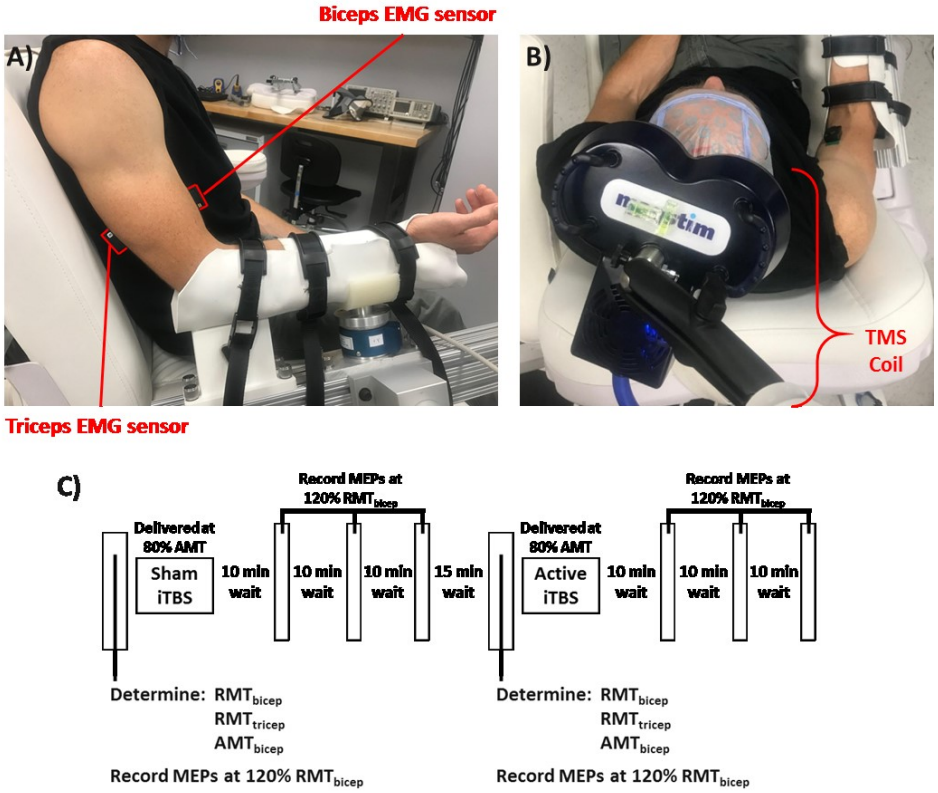

Figure 11: Experimental setup for iTBS sessions; ***A)*** *Participants were seated with their forearm supported in the horizontal plane with EMG sensors place on their biceps and triceps;* ***B)*** *The TMS coil was held tangentially to the scalp and was placed over the biceps representation of the motor cortex. The handle was pointed posteriorly to induce a posterior-anterior current within in the motor cortex;* ***C)*** *Before each application of iTBS, RMTs, AMT, and baseline MEPs were recorded. The intensity of all iTBS pulses was 80% of AMT. MEPs were recorded at 10-minute intervals following iTBS at an intensity of 120% of RMT.*

First, stimulus-response curves were generated to determine the maximal compound muscle action potential (Mmax) values for the biceps and triceps. Next, RMT, AMT, and baseline corticomotor excitability were determined. Baseline corticomotor excitability was determined as the average of MEP amplitudes collected in response to single pulse TMS at an intensity of 120% of RMT every 3 to 5 seconds. iTBS was then delivered, after which MEPs were again recorded at intervals 10, 20, and 30 minutes post-iTBS (Figure 11). This process was performed for both sham and active iTBS with participants receiving a 15-minute break in between. Sham iTBS was always performed prior to active iTBS to prevent the possibility of effects from active iTBS lingering throughout the sham portion of the study.

3.2.3 Electromyography

Electromyography (EMG) data were recorded from the dominant arm of each participant using a Trigno™ Wireless System (Delsys, Natick, MA). Surface EMG electrodes were placed on the long head of the biceps and the lateral head of the triceps. All electrode placement was verified by functional muscle testing. EMG signals were amplified (x1000), bandpass-filtered (20-450 Hz) prior to A/D conversion (Micro 1401 MkII, Cambridge Electron Design, Cambridge, UK), and sampled at 2000 Hz. Prior to electrode placement, the skin cleaned with alcohol wipes.

3.2.4 Maximal compound muscle action potential

The maximal compound muscle action potential (Mmax) was recorded from the biceps and its primary antagonist (triceps brachii) in order to normalize MEPs for each participant and session (R. Nardone et al., 2015). A constant current stimulator (DS7AH, Digitimer Ltd., Hertfordshire, UK) delivered a single pulse electrical stimulus (0.2 ms pulse width) via a bipolar stimulating electrode located at Erb's point (1.25" round, PhysioTech, Richmond, VA). A grounding electrode (1.3" x 2.1", Axelgaard Manufacturing Co., Ltd., Fallbrook, CA) was placed on the acromion. Stimulus-response curves were recorded to determine the Mmax of the resting biceps and triceps. Three electrical stimuli were delivered every five seconds at 5 mA increments until Mmax was reached. The threshold intensity to elicit Mmax was noted. The Mmax value to which MEPs were normalized was determined as the average response to a stimulus corresponding to 1.3 times the threshold intensity delivered across ten trials at 5 second intervals. Data were recorded using custom-written BCI2000 based software (EPOCS) (Schalk, McFarland, Hinterberger, Birbaumer, & Wolpaw, 2004).

3.2.5 Motor threshold evaluation

Single pulse TMS was delivered to the motor cortex contralateral to the resting arm using a Super Rapid Plus stimulator (Magstim, Whitland, UK) via a 70 mm figure-of-eight coil (P/N 3910-00) to determine RMT of the biceps and triceps and AMT of the biceps. The vertex at the intersection of the inion-nasion and inter-aural lines were marked on a cap tied on the participant's head. The coil was held tangentially on the scalp via a support stand with the coil center rotated to induce a posterior-to-anterior cortical current across the central sulcus. The

hotspot for the target muscle was identified as the location evoking the largest peak-to-peak amplitude MEP using the lowest stimulation intensity. RMT was determined as the lowest stimulus intensity that induced MEPs of ≥ 50 μV in at least 5 of 10 consecutive stimuli with the target muscle fully relaxed (P. Rossini & Berardelli, n.d.). AMT was determined as the stimulus intensity that elicited a MEP of ≥ 200 μV in at least 5 of 10 consecutive stimuli recorded during sustained isometric contraction of 10 ± 5% of the participant's maximum effort (Borckardt, Nahas, Koola, & George, 2006). Stimulus intensity was determined using an adaptive parameter estimation by sequential testing (PEST) software developed by Borckardt et al. and participants were provided visual feedback of their effort levels during contractions. Maximum effort was determined from 3 trials of maximum voluntary isometric contractions. Participants were instructed to maximally contract their biceps and hold the contraction for 5 seconds followed by a 1-minute rest period. The greatest root mean squared value of the EMG signal over a 50 ms window was determined for each maximum effort trial and averaged across trials.

3.2.6 Intermittent theta burst stimulation protocol

iTBS was applied using a Magstim Super Rapid Plus stimulator and a 70 mm double air film coil that includes a built-in cooling system to maintain operating temperature. iTBS applied to the biceps hotspot consisted of three pulses presented at 50 Hz, repeated every 200 ms for 2 s at an intensity of 80% of the participant's AMT. Two second bursts were repeated every 8 s for a total of 600 pulses (Huang et al., 2005). In the SCI group, there were 7 instances out of 42 in which the participant's biceps AMT for a given session exceeded 57% MSO, which prevented the ability to deliver iTBS at an intensity of 80% AMT. For these cases, 57% MSO was used to deliver iTBS. For the sham condition, a sham coil (Magstim 70 mm double air film sham coil), looking identical to the active coil and making a similar noise without delivering any active stimulation, was applied to the biceps hotspot. Throughout each session participants were kept unaware of the type of stimulation they were receiving and were presented with nature videos to control engagement.

3.2.7 Pre-hoc power analysis

The sample size of ten participants was derived using an a priori power analysis with the following parameters. The true difference between active and sham protocols of 5% of the nMEP, with a standard deviation of 9%, each participant conducted three sessions, and the

correlation between the differences within an individual is 0.5 (Schoenfeld, 1980). The sample size of ten participants would achieve at least 80% power using a two-sided test of the overall mean using a repeated measures model. While this sample size was able to be achieved in our non-impaired group, our SCI group only had seven participants.

3.2.8 Data processing

MEPs amplitudes were calculated from the biceps EMG data using purpose-written Matlab code (The MathWorks, Inc, Natick, MA) in a time window 12-62 ms following single pulse TMS. The root mean square (RMS) amplitude was calculated for both the evoked response time window and a 50 ms time window prior to single pulse TMS (pre-stimulus). Instances where the pre-stimulus RMS amplitude was greater than the evoked response RMS amplitude, or where voluntary activation was detected, were discarded as muscle activity prior to stimulation can influence MEP amplitudes (Darling, Wolf, & Butler, 2006). Peak-to-peak MEP amplitudes were normalized by the participant's Mmax recorded during the corresponding session, with the ratio multiplied by a scaling factor of 100. Normalized MEPs (nMEPs) served as our measure of corticomotor excitability. The change in corticomotor excitability (ΔnMEP) was defined as the difference between each nMEP collected post-iTBS and the average baseline nMEP amplitude before the corresponding iTBS phase. For the NI group, there was an average of 15 ± 4 measures of $\Delta\mathrm{nMEP}$ for each post-iTBS time point (i.e., 10, 20 and 30 min post-iTBS) per session. For the SCI group, there was an average of 12 ± 5 measures of $\Delta\mathrm{nMEP}$ for each post-iTBS time point per session.

$$\Delta\mathrm{nMEP} = \mathrm{nMEP\ post\ iTBS} - \overline{\mathrm{nMEP\ baseline}}$$

3.2.9 Statistical analyses

When analyzing the effects of active and sham iTBS, a linear mixed effects model was used to assess the difference between baseline and post iTBS nMEP amplitudes with purpose-written R code (R Core Team (2018)). The model had a nested random effect of session within participant to account for potential relationships between nMEPs of the same session or participant, and within each time period post-iTBS. Coil (i.e., active or sham), time (i.e., 10, 20 or 30 minutes post-iTBS), and their interaction were included as fixed effects. A Kenward-Rogers adjustment was used to adjust for estimated random effect parameters (Fitzmaurice, Laird, & Ware, 2011).

To test for correlations between ΔnMEP and RMT values, ΔnMEPs were averaged across all post-iTBS time points (i.e., 10, 20 and 30 minutes post-ITBS) in each session. Due to the non-normality of the data, Spearman's rank order correlation was used to assess the correlation between the average ΔnMEPs for each session and the difference between the RMT of their biceps and triceps ($RMT_{biceps\text{-}triceps}$). RMTs of the triceps ($RMT_{triceps}$) were at or above 100% MSO in the majority of sessions. Thus, the correlation analysis was repeated to assess correlations between the average ΔnMEP and the RMT of the biceps (RMT_{biceps}).

Friedman's test was used to evaluate the repeatability of the baseline nMEP, RMT, and AMT values (Fried, Jannati, Davila-Pérez, & Pascual-Leone, 2017a; Friedman, 1937; Rogasch, Daskalakis, & Fitzgerald, 2013).

3.2.10 Post-hoc analyses

There were instances in both groups in which the participant's RMT_{biceps} exceeded 84% MSO, which prevented the ability to assess MEPs at an intensity of 120% of RMT. For these cases, 100% MSO was used for recording MEPs. However, stimulating at intensities below 120% of RMT may increase MEP variability or even inhibit MEPs [6]. For the NI group, the previously described linear mixed effects model was repeated on the subgroup of instances where RMT_{biceps} were below 84% MSO. This allowed us to assess the results separately for instances where MEPs could be recorded at 120% RMT. Since these instances comprised the majority of the SCI data, the aforementioned subgroups were not created for this population. Instead, the previously described linear mixed effects model of the SCI data was repeated with the inclusion of RMT_{biceps} as a fixed effect. This allowed us to assess the effect the RMT_{biceps} on the recorded nMEPs in this population.

Our initial linear mixed effects model measured instantaneous excitability of the corticomotor system via nMEPS, which are driven by shifts in sodium channel currents and affected by GABA receptor modulation. However, conventional models do not account for the effect of corticomotor conductance potential on nMEPs. Here, corticomotor conductance refers to the synaptic conductance along the corticospinal pathway being stimulated during a given session (Douglas & Martin, 2004; Hodgkin & Huxley, 1952; Klomjai et al., 2015; Schmid, Boll, Liechti, Schmid, & Hess, 1992; U. Ziemann et al., 1996; Ulf Ziemann et al., 2015). Motor thresholds reflect this conductance as they are determined by the synaptic permeability between neurons along the corticomotor tract at rest (RMT) and during activation (AMT), and

unlike MEPs do not change instantaneously. Therefore, the biceps AMT/RMT ratio served as a representation of the corticomotor conductance potential across states of activation (Groppa et al., 2012a; P. M. Rossini et al., 2015). The biceps AMT/RMT ratio was evaluated within a linear mixed effects model to assess a main effect and interactions with time or type of stimulation to account for the effects of corticomotor conductance potential in our model.

Finally, we performed an analysis to investigate potential within-individual effects that may have been masked by the variability of the group wide data (Hinder et al., 2014; Nettekoven et al., 2015; Perellón-Alfonso et al., 2018). Each session was classified as either a “positive response”, “negative response”, or “no-response”. A session was labeled as a “positive response” if the average nMEP after iTBS increased by at least 10% of the baseline nMEP and as a “negative response” if the average nMEP decreased by at least 10% relative to baseline. Otherwise the session was labeled as “no-response”. Fleiss’ kappa (κ) was used to test for relationships among the response label and stimulation type (active or sham) (Banerjee, Capozzoli, McSweeney, & Sinha, 1999; Fleiss & Cohen, 1973; Gisev, Bell, & Chen, 2013).

Chapter 4: The effect of iTBS on corticomotor excitability of the biceps in non-impaired individuals

4.1 Introduction

Non-invasive brain stimulation therapies as an adjunct to physical training may improve motor outcomes in individuals with motor impairments. Priming the corticospinal system with stimulation prior to physical training may further enhance training induced motor re-learning (Gomes-Osman, Tibbett, Poe, & Field-Fote, 2017; Pascual-leone et al., 1991; A. Pascual-Leone et al., 1995; Stoykov & Madhavan, 2015). Increased corticomotor excitability of upper limb muscles is associated with motor learning and skill acquisition (Huang et al., 2005; Klomjai et al., 2015; Priori, Hallett, & Rothwell, 2009). Thus, stimulation therapies that increase corticomotor excitability may aid to improve upper limb function in individuals with motor impairments. Intermittent theta burst stimulation (iTBS) is a form of repetitive transcranial magnetic stimulation (TMS) that can increase corticomotor excitability as measured by motor evoked potential (MEP) amplitudes. iTBS protocols use high frequency TMS at subthreshold intensities with aftereffects lasting up to 30 minutes (Hinder et al., 2014; Klomjai et al., 2015; Suppa, Huang, Funke, Ridding, Cheeran, Di Lazzaro, Ziemann, & Rothwell, 2016). The mechanistic understanding to date is that iTBS can induce long-term potentiation of cortical neurons leading to increased corticomotor excitability (Huang et al., 2005).

A broader understanding of the efficacy of iTBS is needed to inform the design of combinatorial therapies to improve motor function. The majority of prior work examining the effects of iTBS on corticomotor excitability have targeted the distal muscles of the upper limb, particularly the first dorsal interosseous (FDI) (Hinder et al., 2014; Huang et al., 2005; Klomjai et al., 2015; Medina, Marcos-García, Jiménez, Muratore, & Méndez-Suárez, 2017; Priori et al., 2009; Suppa, Huang, Funke, Ridding, Cheeran, Di Lazzaro, Ziemann, & Rothwell, 2016). The FDI is easier to target with TMS relative to more proximal muscles, such as the biceps brachii, as distal muscles have a higher density of corticospinal neurons projecting to the muscle and represent larger motor map areas that are more accessible to TMS (Bawa et al., 2004; Malcolm et al., 2006). While further research targeting the FDI is warranted due to large variability in iTBS induced after-effects within and across individuals, other muscle groups may be in need of rehabilitation and may be appropriate targets for iTBS (Guerra, López-Alonso,

Cheeran, & Suppa, 2018a; Hinder et al., 2014; Klomjai et al., 2015; Peterson et al., 2017; Suppa, Huang, Funke, Ridding, Cheeran, Di Lazzaro, Ziemann, & Rothwell, 2016). For example, after biceps-to-triceps tendon transfer to enable active elbow extension in individuals with tetraplegia, the biceps must undergo training to promote motor re-learning to extend the elbow. Using single pulse TMS, Peterson et al. found a positive relationship between biceps corticomotor excitability and elbow extension strength in individuals with biceps-to-triceps transfer, suggesting that these individuals may benefit from increased biceps corticomotor excitability (Peterson et al., 2017). Previous investigations of iTBS targeting distal muscle (e.g., the FDI) in nonimpaired individuals may not translate to the biceps due to differences in corticospinal control (Neige et al., 2017). As a first step toward application of iTBS to enhance biceps motor re-learning in clinical populations, in the current study we focus on corticomotor excitability of the biceps in nonimpaired individuals.

The purpose of this study was to determine the effect of iTBS on corticomotor excitability of the biceps in non-impaired individuals. In order to assess the reproducibility in iTBS aftereffects, participants were tested across three sessions. Each session, consisting of active and sham stimulation, was separated by three days to prevent the potential for carry over effects. Based on our expectation that iTBS promotes long-term potentiation of cortical neurons (Ah Sen et al., 2017; Suppa, Huang, Funke, Ridding, Cheeran, Di Lazzaro, Ziemann, & Rothwell, 2016), we hypothesized that biceps corticomotor excitability would be increased following active iTBS relative to baseline, and biceps corticomotor excitability would be unchanged following sham iTBS relative to baseline. Further, based on evidence that the difference between the resting motor threshold (RMT) of a flexor muscle and the RMT of its antagonist may determine the efficacy of iTBS (Mirdamadi et al., 2015), we hypothesized that changes in corticomotor excitability after active iTBS would positively correlate with differences between the RMT of the biceps and its antagonist (triceps).

4.2 Results

4.2.1 Change in normalized MEPs post-iTBS

Change in nMEP amplitudes from baseline (i.e., ΔnMEP) did not differ for the active and sham conditions as indicated by no interaction between the type of stimulation and time post-iTBS ($p = 0.915$) in the analysis of the linear mixed effects model (Figure 12).

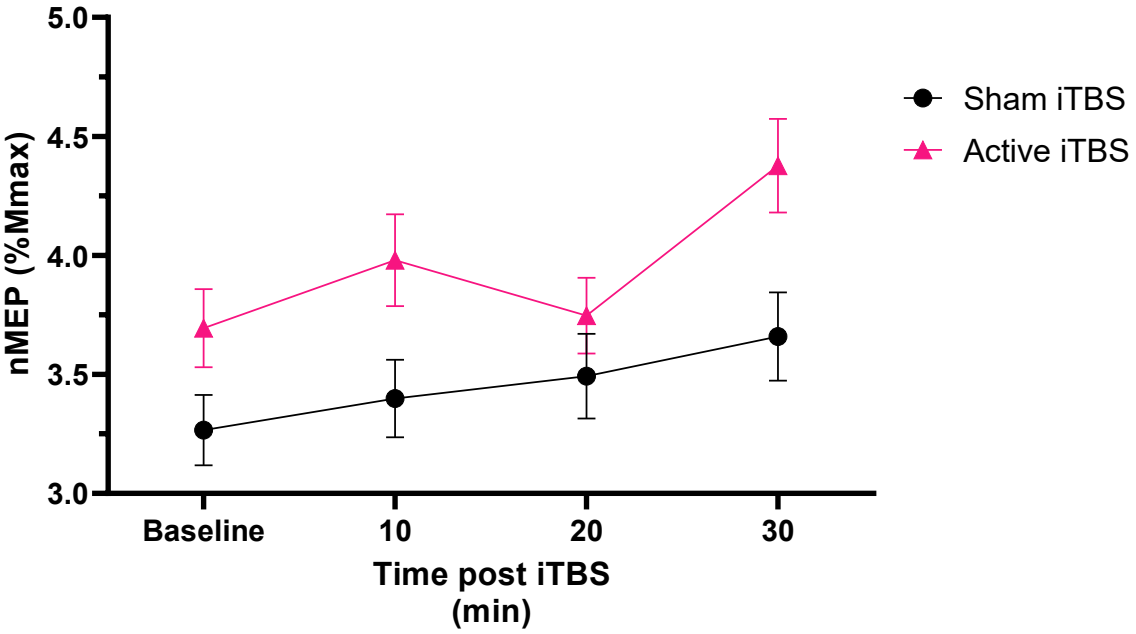

Figure 12: Mean nMEP amplitudes for each time point across all participants for active & sham iTBS. Bars represent one standard error from the mean (SEM). Presented values for sham & active iTBS (time, mean, SEM), Sham: (baseline, 3.266, 0.15), (10, 3.399, 0.16), (20, 3.493, 0.18), (30, 3.659, 0.19); Active: (baseline, 3.694, 0.16), (10, 3.980, 0.19), (20, 3.747, 0.16), (30, 4.377, 0.20).

4.2.2 Correlation between RMT and changes in biceps corticomotor excitability

There was no correlation between the average ΔnMEP and $RMT_{biceps\text{-}triceps}$ ($p = 0.654$ and $p = 0.916$ for sham and active iTBS, respectively) (Figure 13). Also, there was no correlation between the average ΔnMEP and RMT_{biceps} ($p = 0.733$ and $p = 0.956$ for sham and active iTBS, respectively).

In analysis of the data partitioned based on biceps RMT values (one group with RMT < 84% MSO, one group with RMT ≥ 84 % MSO) there was no correlation between the average ΔnMEP and $RMT_{biceps\text{-}triceps}$ in either data set ($p = 0.758$ and $p = 0.973$ for sham and active iTBS, respectively) (Figure 13). There was also no correlation between the average ΔnMEP and RMT_{biceps} in either data set ($p = 0.694$ and $p = 0.882$ for sham and active iTBS, respectively).

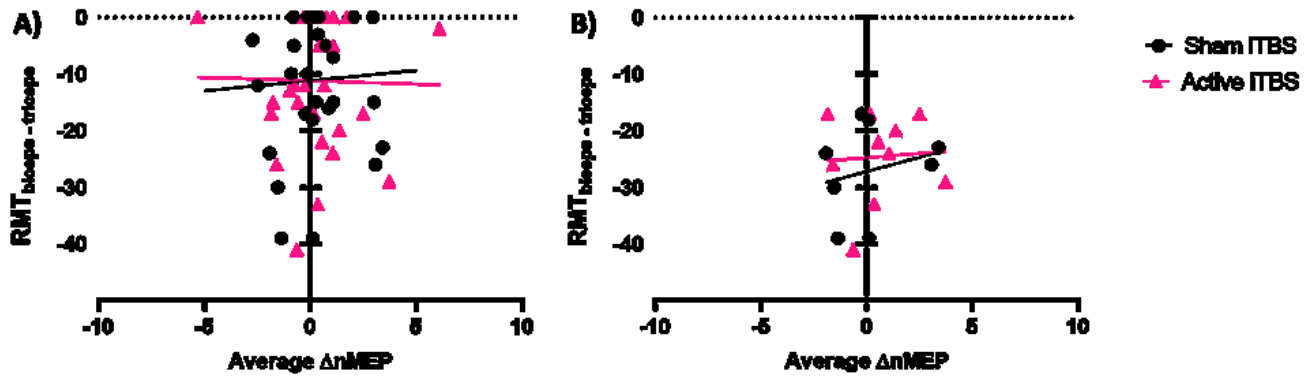

Figure 13: Correlation between average ΔnMEPs and RMT difference; ***A)*** *Data represents all average ΔnMEPs across three sessions plotted against the difference between the RMT of the biceps and RMT of the triceps. No correlation was found for either sham (r = 0.0853) or active iTBS (r = 0.0201);* ***B)*** *Data presented is a subset of the former correlation, showing instances where RMTbiceps was ≤ 84% MSO. No correlation was found in this subgroup for either sham (r = 0.1317) or active iTBS (r = 0.01841).*

Analysis with the linear mixed effect model further supported nMEP amplitudes to not be affected by RMT values ($\chi^2 = 0.5306$, $p = 0.466$). There were also found to be no changes in nMEP amplitude when evaluating the interaction between RMT and iTBS (sham & active) ($\chi^2 = 1.314$, $p = 0.252$) or the interaction of time and iTBS while including RMT values in the linear mixed effects model ($\chi^2 = 0.6767$, $p = 0.411$).

4.2.3 Effect of biceps AMT/RMT ratio on change in nMEP amplitude

The biceps AMT/RMT ratio and nMEP amplitudes were negatively correlated. As the AMT/RMT ratio decreased, nMEP amplitudes increased by 4.474 ($\chi^2 = 18.08$, $p < 0.001$). Evaluation of the interaction of time and stimulation type yielded no change in nMEP amplitude across time between active or sham iTBS ($\chi^2 = 2.44$, $p = 0.118$). However, the slope of the line relating nMEP amplitude to the AMT:RMT ratio was increased by active iTBS relative to sham by 3.23 ($\chi^2 = 14.697$, $p < 0.001$). This suggests that the negative relationship between AMT/RMT ratio and nMEP amplitude was depressed by active iTBS stimulation (Figure 14).

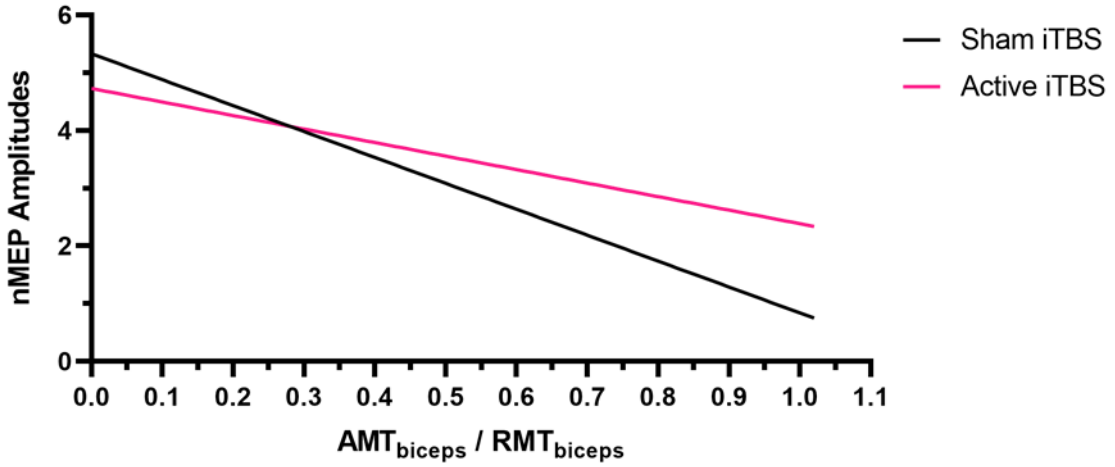

Figure 14: Relationship between AMT/RMT ratio and nMEP amplitude; *Data shows a negative relationship between nMEP amplitude and the AMT/RMT ratio, with the magnitude of this negative trend being reduced by active iTBS. The nMEP amplitudes were modeled across AMT/RMT ratios ranging from 0 to 1 based on recorded threshold values.*

4.2.4 Effect of iTBS on nMEP Variability

There was no change in standard deviation of nMEP amplitude after iTBS when compared to baseline or after sham stimulation at any time point or across all time points post stimulus (for 10 minutes post-iTBS, 20 minutes post-iTBS, and 30 minutes post-iTBS, p = 0.805, 0.120, 0.978 respectively).

4.2.5 Responder analysis

There was no relationship between session and response label (κ_{Active} = 0.09, κ_{Sham} = 0.04) (Table 3). Furthermore, we found that an individual's responsiveness to active iTBS was not related to responsiveness to sham iTBS (κ = 0.44). As found with other studies, responsiveness to active iTBS was not predicated on the response to sham (Hinder et al., 2014; Perellón-Alfonso et al., 2018).

Table 3:*Session response: Counts of each responder label for participants in each session are given for active and sham iTBS with a 10% cutoff value.*

	Session 1	Session 2	Session 3	Total
Sham iTBS				
Positive Responders	7	5	3	15
Negative Responders	3	2	5	10
Non-Responders	0	3	2	5
Active iTBS				
Positive Responders	3	7	4	14
Negative Responders	6	1	5	12
Non-Responders	1	2	1	4

4.2.6 Repeatability of nMEP, AMT, and RMT

Friedman's test revealed that the AMT was repeatable across sessions (p_{AMT} = 0.0546), while biceps RMT and baseline nMEPs were not repeatable across sessions (p_{RMT_biceps} = 0.0061, p_{nMEPs} < 2.2e-16) (Table 4).

Table 4. *Baseline Metrics: Values represent the mean and standard deviations of the baseline metrics collected prior to iTBS. RMT: resting motor threshold; AMT: active motor threshold; nMEP: normalized MEPs*

	Session 1	Session 2	Session 3
Sham iTBS			
RMT_{biceps}	89.5 ± 9	87.6 ± 13	88.4 ± 14
$RMT_{triceps}$	100.0 ± 0	99.3 ± 2	99.5 ± 2
AMT_{biceps}	60.3 ± 8	58.5 ± 9	55.1 ± 9
Baseline nMEP	3.210 ± 3.00	3.686 ± 3.66	2.972 ± 2.45
Active iTBS			
RMT_{biceps}	89.0 ± 10	90.6 ± 12	86.1 ± 14
$RMT_{triceps}$	100.0 ± 0	100.0 ± 0	99.4 ± 2
AMT_{biceps}	59.8 ± 6	60.0 ± 6	50.0 ± 9
Baseline nMEP	4.480 ± 4.14	3.437 ± 2.97	3.061 ± 2.94

4.3 Discussion

The primary objective of this study was to determine the effect of iTBS on the corticomotor excitability of the biceps as measured by MEPs in response to TMS. Secondary objectives were to assess the reproducibility of iTBS effects across three sessions, and to determine whether the difference between the RMT of the biceps and triceps was predictive of changes in biceps corticomotor excitability. We hypothesized that biceps corticomotor excitability (i.e., biceps MEPs normalized to biceps Mmax) would be increased following active iTBS relative to baseline, and biceps corticomotor excitability would be unchanged following sham iTBS relative to baseline. This hypothesis was not supported; there was no change in biceps nMEPs after either active or sham iTBS in assessments 10, 20, and 30 minutes post-stimulation. We also hypothesized that changes in biceps corticomotor excitability after active iTBS would positively correlate with differences between the RMT of the biceps and its antagonist (triceps). This hypothesis was not supported; there was no correlation between the $RMT_{biceps\text{-}triceps}$ values and the average change in nMEPs after active or sham iTBS. These results suggest that in our cohort of nonimpaired individuals, iTBS targeting the biceps failed to induce long-term potentiation of cortical neurons such that biceps corticomotor excitability was not affected by iTBS. While improvement of rehabilitation outcomes is the long-term context of this research, it would not appear that iTBS would directly aid in motor learning across the entirety of our non-impaired population.

Considering the effects of iTBS on cortical regions projecting to more distal muscles of the upper limb, our results support that the magnitude and variability of changes evoked by iTBS depend on the cortical region targeted (Guerra et al., 2018a; P. G. Martin et al., 2006). A comprehensive meta-analytic review across studies conducted in humans reported iTBS yields MEP increases lasting up to 30 minutes (Chung, Hill, Rogasch, Hoy, & Fitzgerald, 2016b). However, the predominant targets of iTBS in these studies were distal muscles of the upper limb, particularly the FDI. The lack of an effect of iTBS on biceps corticomotor excitability suggests this proximal muscle is less susceptible to long-term potentiation induced by iTBS relative to distal muscles. This may be due to the method by which iTBS induces synchronous activity in the neural network, which is reflected by an increase in the amplitude of later I-waves. The facilitation of later I-waves is primarily related to the monosynaptic corticospinal tracts (Klomjai et al., 2015; U. Ziemann et al., 1996). Direct monosynaptic corticospinal projections are more prominent for hand muscles as evidence of greater I-wave facilitation

relative to the biceps in response to paired-pulse TMS (D. Burke et al., 1993; Devanne, Lavoie, & Capaday, 1997; P. G. Martin et al., 2006; Raffaele Nardone et al., 2015; Sakai et al., 1997; Ulf Ziemann et al., 1998). Thus, the negative findings in the current study targeting the biceps are likely driven by differences in corticospinal control between the proximal and distal muscles.

The lack of effects on biceps corticomotor excitability after TBS is not limited to the current study. Continuous theta burst stimulation (cTBS) is another form of TBS which has been found to reduce the excitability of the cortical region projecting to the FDI (Huang et al., 2005; Jannati et al., 2019a; P. G. Martin et al., 2006). Martin et al. found that cTBS had no effect on biceps corticomotor excitability, despite observing large and long-lasting inhibition in most participants when the FDI was targeted (P. G. Martin et al., 2006). Our results were similar to the findings of Martin et al, with high variability in the biceps MEPs both before and after theta burst stimulation. While the mechanisms of iTBS and cTBS differ, the high variability in MEPs could be a reason for the lack of group findings after either TBS protocol (Darling et al., 2006; Guerra, López-Alonso, Cheeran, & Suppa, 2018b; Hashemirad, Zoghi, Fitzgerald, & Jaberzadeh, 2017; P. G. Martin et al., 2006). Our analysis of the changes in standard deviations after iTBS indicate that the variability in MEP amplitudes is not affected by iTBS and is most likely due to inherent differences across and even within individuals. It is postulated that much of this variability is linked to factors such as the preferential activation of different intracortical networks, history of physical activity, timing, age, and genetic differences potentially including brain-derived neurotrophic factor (BDNF) genotype (Fried, Jannati, Davila-Pérez, & Pascual-Leone, 2017b; Guerra et al., 2018b; Hamada et al., 2013; Hashemirad et al., 2017; M. C. Ridding & Ziemann, 2010; ter Braack, de Goede, & van Putten, 2019). While accounting for these factors was not in the scope of this pilot study, within-participant variability was assessed using a session response analysis analogous that performed by Perellon-Alfonso et al (Perellón-Alfonso et al., 2018). Similar to their findings, our results showed no differences between the number of responses to active or sham iTBS.

Assessing the repeatability of motor thresholds and baseline nMEP amplitudes can aid in understanding the effects of TBS and are particularly valuable considering the large variability in biceps MEPs. RMT and AMT represent the excitability of an individual's corticomotor tract when at rest and activated, respectively, and can be used to evaluate the excitability of the cortical motor region prior to delivering iTBS (Groppa et al., 2012a; Klomjai et al., 2015; P. M. Rossini et al., 2015). When at rest, the corticomotor tract of a muscle can be

characterized as being relative disorganized as the membrane potential of each neuron along the pathway is not uniform. However, muscle contraction can provide the tract with a greater degree of organization as it increases the membrane conductance of the neurons and places their membrane potentials in a more primed state to depolarize. Thus, AMT thresholds can typically be attained at lower stimulus intensities than RMT (Groppa et al., 2012b; Paulus et al., 2008; P. M. Rossini et al., 2015; Ulf Ziemann et al., 2015).

Some studies which have targeted TBS to the FDI have found baseline nMEPs, AMT, and RMT measurements to be repeatable across sessions (Fried et al., 2017a; Jannati et al., 2019b; Perellón-Alfonso et al., 2018; Vallence et al., 2015; Vernet et al., 2014b). However, in this study only the AMT of the biceps was found to be repeatable. This suggests that muscle activation provides a more uniform baseline for comparing the response to TMS across muscles, as motor regions are in a more similar state when activated than when at rest. Additionally, our post-hoc analysis found that biceps corticomotor excitability was negatively correlated with an individual's biceps AMT/RMT ratio, and this negative effect was reduced by active iTBS. At higher AMT/RMT ratios, active iTBS increased nMEP amplitudes relative to sham, indicating that there were nonuniform changes in the response to active iTBS across these ratios relative to sham. Low AMT/RMT ratios would represent a conductive corticospinal system with not much potential for change, while high ratios would represent a less conductive system which would be more likely to benefit from iTBS. Thus, the AMT/RMT ratio, used to represent inherent conductance, may be a predictive measure to evaluate the potential for iTBS to increase biceps corticomotor excitability.

Chapter 5: The effect of iTBS on corticomotor excitability of the biceps in individuals with low cervical SCI

5.1 Introduction

For individuals who have experienced an incomplete spinal cord injury (SCI), improving sensory and motor function is a crucial part of rehabilitation efforts in order to enhance their quality of life. The remaining functional neurons within the corticospinal tract are able to undergo reorganization in order to preserve some motor function (Cramer et al., 2011; Alvaro Pascual-Leone et al., 2005), although considerable amounts of physical therapy are still needed. For individuals with tetraplegia, upper limb function is frequently rated as the most desired ability to be regained due to its importance in performing daily activities (Anderson et al., 2009). While physical therapy is able to promote motor re-education of these impaired muscles, the damage to the corticospinal system can often limit the potential functional outcomes (Devivo, 2012).

Implementing a form of repetitive transcranial magnetic stimulation (rTMS) as an adjunct to physical therapy may improve motor re-education in individuals with tetraplegia. When targeted to the motor region of the brain in individuals with motor impairments, rTMS methods have been found to induce LTP- and LTD-like mechanisms in the remaining functional neurons (M. C. Ridding & Ziemann, 2010). These mechanisms are linked to increases in corticomotor excitability, as measured by motor evoked potential (MEP) amplitudes, and lead to improvements in an individual's sensory and motor function (Michael C. Ridding & Rothwell, 2007). However, studies have used a variety of stimulation parameters (intensities, frequency, number of pulses, etc), making findings variable and difficult to compare (Tazoe & Perez, 2015).

Intermittent theta burst stimulation (iTBS) is a form of rTMS that has been shown to increase corticomotor excitability. Studies which have targeted the first dorsal interosseous (FDI) and flexor carpi radialis (FCR) in non-impaired individuals have shown iTBS to cause an increase in MEP amplitudes (Hinder et al., 2014; Huang et al., 2005; Mirdamadi et al., 2015). However, due to the corticospinal reorganization that occurs after injury, the observed effects of iTBS in a non-impaired population cannot necessarily be translated to those with tetraplegia. There have been a limited number of studies which have investigated the effects of iTBS on

corticomotor excitability in those with spinal cord injury. Of these studies, one which targeted the FCR found MEPs to be reduced in the majority of instances post stimulation (Fassett et al., 2017). While further research targeting these distal upper-limb muscles is warranted due to variability in the induced after affects seen across and within group populations, there are other muscle groups which may benefit from iTBS (Hinder et al., 2014; Klomjai et al., 2015; Peterson et al., 2017). In individuals with tetraplegia, the biceps brachii are less likely to be as impaired compared to distal upper limb muscles (i.e. the FDI and FCR) (Armin Curt, Keck, & Dietz, 1998). The biceps can also be used for tendon/muscle transfer to enable active elbow extension in these individuals. Using single pulse TMS, Peterson et al. found a positive relationship between corticomotor excitability and elbow extension strength in individuals with biceps-to-triceps transfer (Peterson et al., 2017). Therefore, the biceps may be a more relevant therapeutic target for iTBS in individuals with tetraplegia.

The purpose of this study was to determine the effect of iTBS on corticomotor excitability of the biceps in individuals with tetraplegia. In order to assess reproducibility in iTBS aftereffects, participants were tested across three sessions. Each session, consisting of active and sham stimulation, was separated by three days to prevent the potential for carry over effects. Based on our expectation that iTBS promotes long-term potentiation of cortical neurons (Suppa, Huang, Funke, Ridding, Cheeran, Di Lazzaro, Ziemann, Rothwell, et al., 2016), we hypothesized that biceps corticomotor excitability would be increased following active iTBS relative to baseline, and biceps corticomotor excitability would be unchanged following sham iTBS relative to baseline. Further, based on evidence that the difference between the resting motor threshold (RMT) of a target flexor muscle and the RMT of its antagonist may determine the efficacy of iTBS (Mirdamadi et al., 2015), we hypothesized that changes in corticomotor excitability after active iTBS would positively correlate with differences between the RMT of the biceps and its antagonist (triceps).

5.2 Results

5.2.1 Change in normalized MEPs post-iTBS

The change in nMEP amplitudes from baseline (i.e., ΔnMEP) differed between active and sham stimulations as indicated by an interaction between the type of stimulation and time post-iTBS ($p = 0.0104$) in the analysis of the linear mixed effects model (Figure 15).

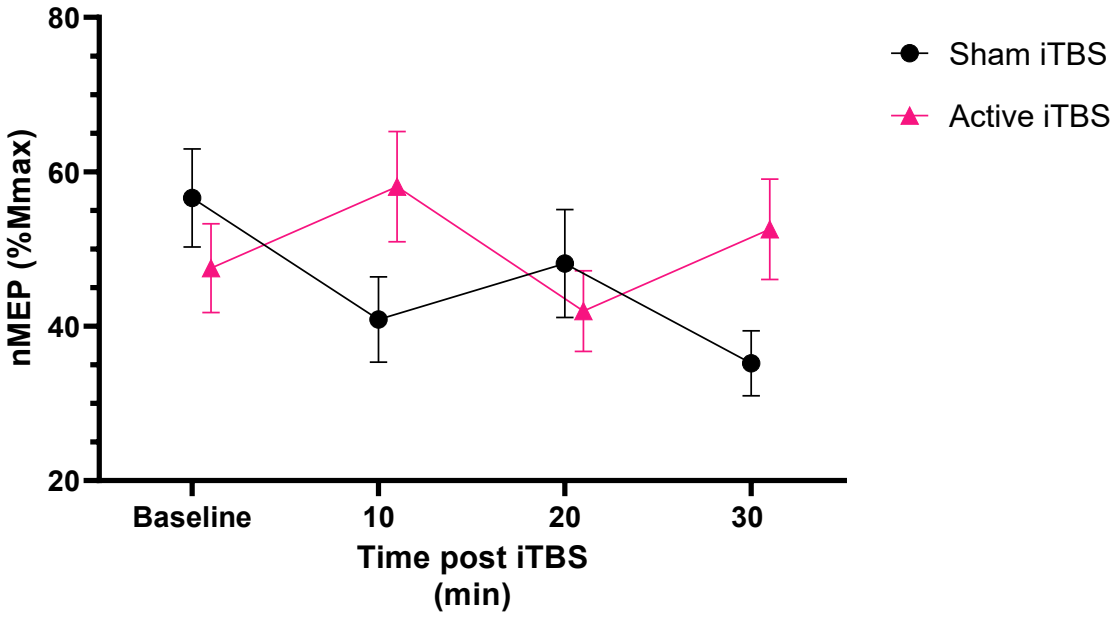

Figure 15. Mean nMEP amplitudes for each time point across all participants for active & sham iTBS. Bars represent one standard error from the mean (SEM). Presented values for sham & active iTBS (time, mean, SEM), Sham: (baseline, 56.603, 6.37), (10, 40.858, 5.54), (20, 48.107, 7.01), (30, 35.216, 4.22); Active: (baseline, 47.523, 5.74), (10, 58.092, 7.15), (20, 41.952, 5.22), (30, 52.555, 6.50).

5.2.2 Correlation between motor thresholds and changes in corticomotor excitability

There was no correlation between the average ΔnMEP and $RMT_{biceps\text{-}triceps}$ ($p = 0.613$ and $p = 0.0817$ for sham and active iTBS, respectively) (Figure 16). There was also no correlation between the average ΔnMEP and RMT_{biceps} ($p = 0.613$ and $p = 0.0841$ for sham and active iTBS, respectively). Furthermore, analysis with the linear mixed effect model further supported nMEP amplitudes to not be affected by RMT values ($\chi^2 = 2.8414$, $p = 0.0919$).

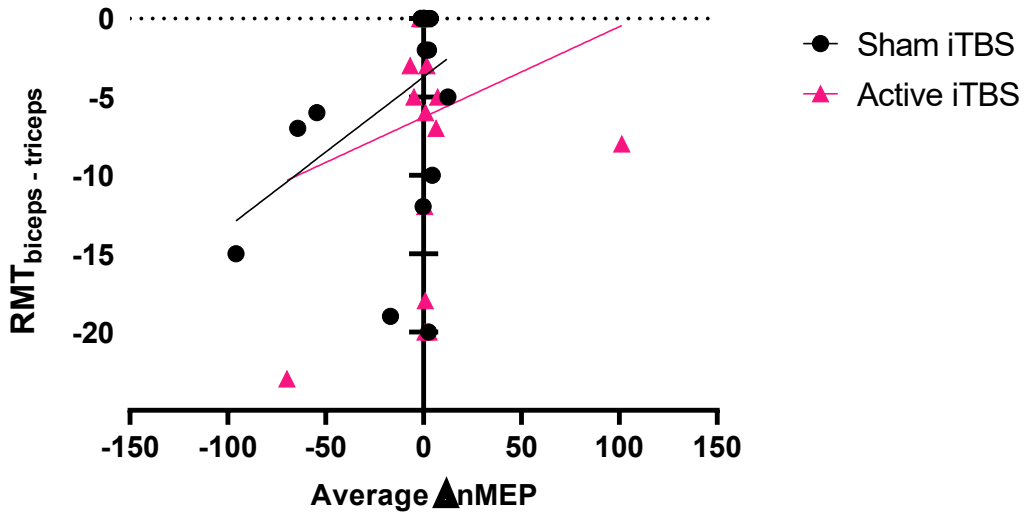

Figure 16. Correlation between the average ΔnMEPs and the RMT difference; Data represents all average ΔnMEPs across three sessions plotted against the difference between the RMT of the biceps and RMT of the triceps. No correlation was found for either sham (r = 0.1172) or active iTBS (r = -0.3886).

5.2.3 Effect of AMT/RMT ratio on change in nMEP

The linear mixed effects model revealed that the slope of the line relating nMEP amplitude to the AMT:RMT ratio was decreased by active iTBS relative to sham by 68.4679 (χ^2 = 15.21, $p < 0.001$). This suggests that those with lower AMT/RMT ratios experienced the greatest increase in nMEP amplitude after active iTBS (Figure 17).

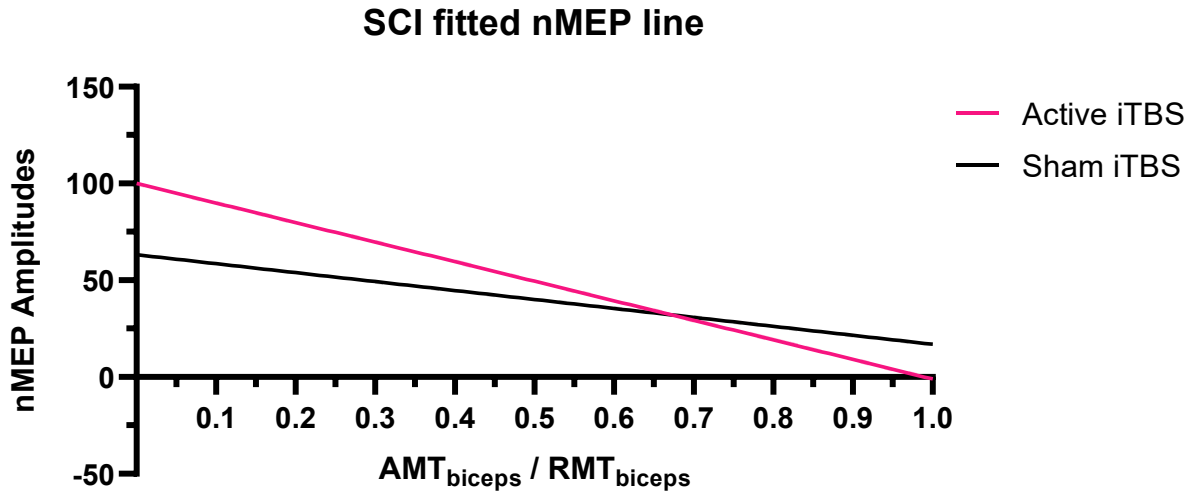

Figure 17. Relationship between AMT/RMT ratio and nMEP amplitude; *Data shows no relationship between nMEP amplitude and the AMT/RMT ratio. The nMEP amplitudes were modeled across AMT/RMT ratios ranging from 0 to 1 based on recorded threshold values.*

5.2.4 Response & repeatability analysis

There was no relationship between session and response label (κ_{Active} = -0.3315, κ_{Sham} = -0.3125) (Table 5). Furthermore, we found that an individual's responsiveness to active iTBS was not related to responsiveness to sham iTBS (κ = 0.0295). As found with other studies, responsiveness to active iTBS was not predicated on the response to sham (Hinder et al., 2014; Perellón-Alfonso et al., 2018). Friedman's test further revealed that all baseline metrics were repeatable across sessions (p_{RMT} = 0.206, p_{AMT} = 0.317, $p_{baseline\ nMEPs}$ =0.0661) (Table 6).

Table 5. *Session response: Counts of each responder label for participants in each session are given for active and sham iTBS with a 10% cutoff value.*

	Session 1	Session 2	Session 3	Total
Sham iTBS				
Positive Responders	2	3	4	9
Negative Responders	3	3	2	8
Non-Responders	2	1	1	4
Active iTBS				
Positive Responders	2	3	5	10
Negative Responders	4	2	1	7
Non-Responders	1	2	1	4

Table 6. *Baseline Metrics: Values represent the mean and standard deviations of the baseline metrics collected prior to iTBS. RMT: resting motor threshold; AMT: active motor threshold; nMEP: normalized MEPs*

	Session 1	Session 2	Session 3
Sham iTBS			
RMT_{biceps}	92.7 ± 9	97.0 ± 6	96.3 ± 5
$RMT_{triceps}$	100.0 ± 0	100.0 ± 0	100.0 ± 0
AMT_{biceps}	64.7 ± 20	64.1 ± 29	61.0 ± 20
Baseline nMEP	85.506 ± 123.40	71.367 ± 100.77	4.0490 ± 5.15
Active iTBS			
RMT_{biceps}	92.7 ± 9	92.3 ± 9	96.1 ± 5
$RMT_{triceps}$	100.0 ± 0	100.0 ± 0	99.7 ± 1
AMT_{biceps}	67.9 ± 17	66.7 ± 21	62.1 ± 19
Baseline nMEP	68.593 ± 102.77	63.943 ± 114.19	6.604 ± 7.20

5.3 Discussion

The primary objective of this study was to determine the effect of iTBS on the corticomotor excitability of the biceps in individuals with tetraplegia, as measured by MEPs in response to TMS. Secondary objectives were to assess the reproducibility of iTBS effects across three sessions, and to determine whether the difference between the RMT of the biceps and triceps was predictive of changes in biceps corticomotor excitability. We hypothesized that biceps corticomotor excitability (i.e., biceps MEPs normalized to biceps Mmax) would be increased following active iTBS relative to baseline, and biceps corticomotor excitability would be unchanged following sham iTBS relative to baseline. Results showed there to be a significant increase in biceps nMEPs over time in active iTBS when compared to sham. We also hypothesized that changes in biceps corticomotor excitability after active iTBS would positively correlate with differences between the RMT of the biceps and its antagonist (triceps). This hypothesis was not supported; there was no correlation between the $RMT_{biceps-triceps}$ values and the average change in nMEPs after active or sham iTBS. These results suggest that in our cohort of individuals with spinal cord injury, active iTBS targeting the biceps induced more LTP-like effects in the cortical neurons compared to sham, such that the biceps corticomotor excitability was increased.

The results from this pilot study provide further support that corticomotor excitability is modifiable in individuals with incomplete spinal cord injury. This supports the findings from the study performed by Fassett et al. in which iTBS was targeted to the FCR in individuals with incomplete cervical spinal cord injury, although their results showed MEP amplitudes to be reduced following iTBS (Fassett et al., 2017). These different effects of iTBS could be due to differences in the targeted cortical motor region. Previous studies, including our previously discussed study, have indicated that changes induced by iTBS in non-impaired individuals depend on the cortical region targeted due to inherent differences in corticospinal control among muscles (P. G. Martin et al., 2006). The findings from this study suggest that this may also be true for individuals with incomplete spinal cord injury, and that the response to iTBS could be further affected by the degree of damage to a muscle's corticospinal tracts after injury. After a cervical spinal cord injury, the distal muscles of the upper limb (i.e. FCR or abductor digiti minimi) are likely to be more impaired than the more proximal muscles (i.e. biceps brachii) (Armin Curt et al., 1998). Therefore, while distal muscles may be more suitable targets for iTBS in non-impaired individuals, the degree of impairment that occurs in distal

muscles after a low cervical spinal cord injury could make more proximal muscle, such as the biceps, a more suitable target for iTBS (Bruehlmeier et al., 1998; Levy et al., 1990; Topka et al., 1991).

Some studies have suggested that the elevated motor thresholds associated with individuals with spinal cord injury are a contributing factor for their responsiveness to rTMS protocols. The rationale is that these higher thresholds result in higher stimulation intensities, which will cause changes to corticomotor excitability regardless of the type of rTMS protocol used (Berardelli et al., 1998; Perez et al., 2005). Our results do not support this theory as there was no correlation found between RMTs of the biceps and the change in corticomotor excitability. Furthermore, our post-hoc analysis found that the interaction between the AMT/RMT ratio and coil had a significant effect on nMEPs, suggesting that those with low AMT/RMT ratios were more likely to benefit from iTBS than those with high ratios. Muscle contraction is known to increase the membrane conductance of the postsynaptic neurons as well as cortical organization as more synapses are primed to depolarize, which is why AMT values are typically found to be lower than RMT values (P. M. Rossini et al., 2015). Therefore, the AMT/RMT ratio could be an indicator of the potential for change in conductance within the corticospinal tracts of a given muscle. For individuals with low cervical spinal cord injury, low ratios would indicate that the corticospinal tract of the muscle has potential to increase its conductance from iTBS, while high ratios would indicate that the corticospinal tract of the muscle is less likely to respond to iTBS. Thus, this ratio could be used as a predictive measure to determine who would benefit most from iTBS.

Chapter 6: Conclusions and future directions

For individuals with a low cervical spinal cord injury, upper limb function is a crucial ability for performing daily activities and allowing for an autonomous life. While physical therapy can help improve and maintain motor function of these muscles after injury, the damage to the corticospinal system often limits the potential functional outcomes. Thus, methods of neuromodulation which increase the corticomotor excitability of these muscles may serve as a valuable adjunct to physical therapy, as these increases are associated with improved motor learning and skill acquisition. iTBS is a non-invasive neuromodulation technique which has previously been found to increase corticomotor excitability of distal upper limb muscles, such as the FDI, in non-impaired individuals. However, a better physiological understanding of the effects of iTBS is needed before combinatorial therapies can be achieved. This requires examining the effects of iTBS in different muscle groups and in muscles affected by spinal cord injury.

6.1 Work completed

The primary objectives of these studies were to determine if iTBS had an effect on the bicep's corticomotor excitability, as measured by nMEPs, in non-impaired individuals and those with low cervical spinal cord injury. Secondary objectives were to assess correlations between the change in corticomotor excitability and the difference between the RMT of the biceps and triceps, as well as the reproducibility of iTBS aftereffects. Ten non-impaired individuals and seven individuals with low cervical spinal cord injury participated in the respective studies. Both studies consisted of testing participants across three sessions, each containing both sham and active iTBS. MEPs were collected before and after iTBS and were analyzed with a linear mixed effects model. The expectation was that in both populations, active iTBS would increase nMEP amplitudes and sham iTBS would have no effect.

6.2 Key takeaways

In our population of non-impaired individuals, iTBS was found to have no effect on the biceps corticomotor excitability, as demonstrated by a lack of change in nMEP amplitudes.

Additionally, changes in corticomotor excitability were not found to be correlated with the difference between the RMT of the biceps and triceps. Considering previous studies have found iTBS to increase corticomotor excitability in distal muscles of the upper limb, our results support that the effects of iTBS depend on the targeted cortical region (Guerra et al., 2018b; P. G. Martin et al., 2006). This is likely due to the inherent differences in corticospinal control that exist between proximal and distal muscles of the upper limb. However, despite the lack of a group effect of iTBS, our post-hoc analysis revealed that there was a non-uniform response to active iTBS. The linear mixed effects model revealed that the nMEP amplitude was negatively correlated with the AMT/RMT ratio and that there was a significant interaction between the AMT/RMT ratio and coil. This resulted in a 3.23 increase in the slope of the line relating nMEP amplitude to the AMT/RMT ratio after active iTBS relative to sham. This suggests that relative to sham iTBS, active iTBS induced greater changes in nMEPs at higher AMT/RMT ratios than at lower ratios.

In our population of individuals with low cervical spinal cord injury, active iTBS was found to increase biceps corticomotor excitability relative to sham, as reflected by an increase in nMEP amplitudes. While a previous study which targeted the FCR found iTBS to decrease MEPs in individuals with incomplete cervical spinal cord injury, our results were similar in that they demonstrate the potential for iTBS to modify corticomotor excitability in this population (Fassett et al., 2017). The difference in the effect of iTBS between our studies could be due to differences in the level of impairment between the distal and more proximal muscles of the upper limb, with more proximal muscles being less impaired after cervical spinal cord injury and more likely to have a positive response to iTBS (Armin Curt et al., 1998). Therefore, the effects of iTBS in individuals with cervical spinal cord injury may depend on the targeted corticomotor region, with the biceps being a more suitable target in these individuals. While there was no correlation between these changes in corticomotor excitability and the difference between the RMT of the biceps and triceps, our post-hoc analysis revealed that there was a significant interaction between the AMT/RMT ratio and coil. This resulted in a 68.47 decrease in the slope of the line relating nMEP amplitude to the AMT/RMT ratio after active iTBS relative to sham. This suggests that relative to sham iTBS, active iTBS induced greater changes in nMEPs at lower AMT/RMT ratios than at higher ratios.

The work from this thesis showed two significant findings. First, the studies showed that the aftereffects of iTBS targeted to the biceps differ between non-impaired individuals and those with low cervical spinal cord injury. Secondly, the effect of iTBS on biceps nMEP

amplitude was found to be correlated with the AMT/RMT ratio of the biceps in both populations. These results provide insight into the efficacy of targeting iTBS to the biceps, as well as a possible predictive measure to evaluate who may benefit most from iTBS.

6.3 Limitations

A low peak intensity of our biphasic magnetic stimulator and coil resulted in the majority of our participants having RMT values ≥ 84% MSO, which prevented them from being stimulated with the proper intensity (120% RMT) during MEP collection. This also limited our ability to evaluate a correlation between $RMT_{biceps\text{-}triceps}$ and nMEP amplitude as the RMT of the triceps was at or above 100% MSO. This issue could be addressed by using a monophasic stimulator to evaluate motor thresholds and collect MEPs as the RMT of the biceps as determined by a monophasic coil are typically 50-60 %MSO (P. M. Rossini et al., 2015). However, incorporating RMT_{biceps} values as a main effect in our linear mixed effects model showed that there was no difference between the subgroup of individuals with RMT_{biceps} values of ≥ 84% MSO and the rest of the participants, suggesting that this limitation did not have an effect on our collected MEPs.

Across both of our studies, there was a high degree of variability in the recorded MEPs. This variability is commonly seen across rTMS studies and thought to contribute to the lack of group findings (Darling et al., 2006; Guerra et al., 2018b; Hashemirad et al., 2017; P. G. Martin et al., 2006). Some research suggests that this variability is primarily caused by inherent fluctuations in neural excitability at both the cortical and spinal level (Jung et al., 2010). This variability is also thought to be linked to other factors such as intracortical differences, history of physical activity, timing, age, and genetic differences potentially including brain-derived neurotrophic factor (BDNF) genotype (Fried et al., 2017b; Guerra et al., 2018b; Hamada et al., 2013; Hashemirad et al., 2017; M. C. Ridding & Ziemann, 2010; ter Braack et al., 2019). While accounting for all these factors was not within the scope of these pilot studies, an attempt was made to account for variations in cortical engagement and timing by presenting participants with nature videos throughout each session and maintaining consistent timing of sessions. Accounting for additional factors of variability would need to be considered when designing the structure of future studies.

6.4 Future directions

The findings from these studies provide several opportunities for further research. First, additional studies are needed to help understand the variable responses that are associated with iTBS across muscles and individuals. These could be conducted through computational modeling or additional iTBS studies which investigate the effect of the AMT/RMT ratio in other muscles. Furthermore, the positive findings seen in individuals with spinal cord injury provide a rationale that iTBS could be used to help improve motor function within this population. This could be of great benefit to individuals who have had a tendon transfer if we can demonstrate a similar effect of iTBS in transferred muscles.

Despite the potential for iTBS to increase corticomotor excitability, a major limitation of existing studies is that the response to iTBS can be highly variable across individuals. Research suggests this variability in response is linked to differences in the intracortical networks activated by TMS (Hamada et al., 2013). To develop a better understanding of the roles these networks play in the responsiveness of an individual to iTBS, future research could consist of developing computational brain models of non-impaired individuals. These models would allow us to investigate how brain anatomy impacts the TMS-induced electric fields that act on the cortical neural fiber tracts of different muscles. If these induced electric fields can then be correlated with changes in MEP amplitudes following iTBS, this model would help serve as a basis for identifying motor regions and individuals that are more likely to respond to iTBS.

While there are differences in corticospinal control among muscles, membrane conductance is a common metric that can be represented by the motor thresholds across all muscles in all individuals. The findings from our studies suggest that the difference in membrane conductance between a muscle's active and rest state may serve as an indicator of how much potential for change in excitability there is within the corticospinal tracts associated with that muscle. However, this has only been demonstrated in the biceps thus far and would need to be demonstrated in other muscles as well. Therefore, a future study should further investigate if the AMT/RMT ratio can serve as a predictive measure for the response to iTBS in other muscles as well, such as the FDI.

As discussed earlier, a tendon or nerve transfer surgery serves as an inventive method for restoring muscle functions that were lost due to spinal cord injury. However, the donor muscle or nerve must undergo extensive motor re-education and strength training after surgery

for optimal outcomes to be achieved. As a result, most individuals do not see improvements in their motor function until at least 12 to 18 months after surgery (Fox et al., 2015). With increases in corticomotor excitability being associated with improvements in motor learning, a future research study could determine the effect of iTBS on corticomotor excitability in individuals with spinal cord injury who have undergone a tendon or nerve transfer. This would allow us to determine if iTBS could be used as an adjunct to physical rehabilitation after a tendon transfer and help individuals see improvements in their motor functions sooner after surgery.

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Appendix A: Sample of Recorded MEPs

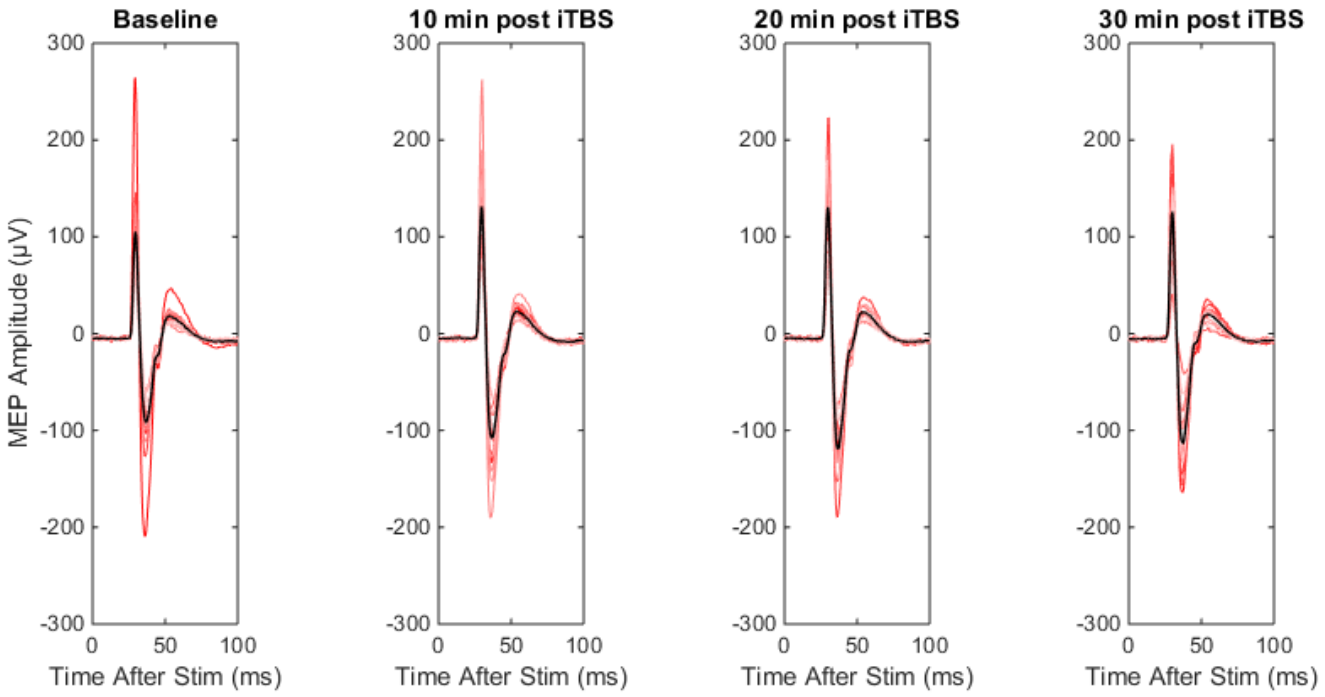

Figure 18. Sample of recorded MEPs from one of our non-impaired participants. Red represents the recorded MEPs during the time period, black represents the average MEP for that time period.

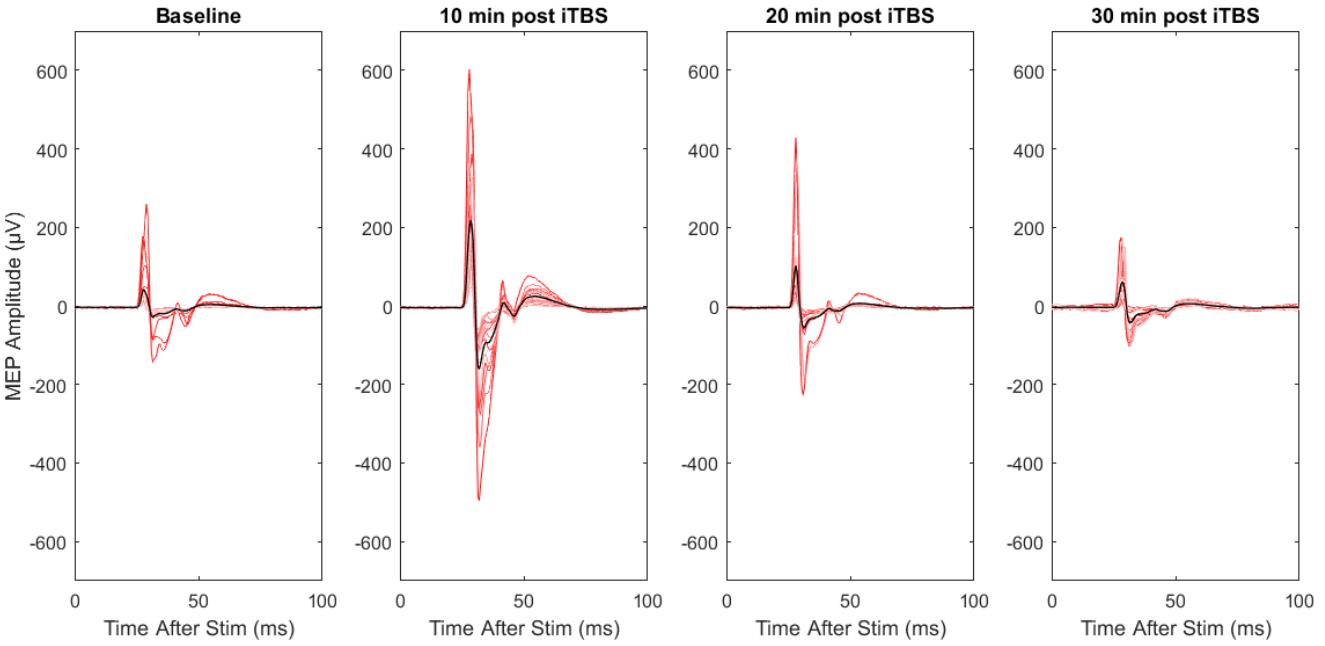

Figure 19. Sample of recorded MEPs from one of our low cervical SCI participants. Red represents the recorded MEPs during the time period, black represents the average MEP for that time period.

Appendix B: Conference Abstracts

Effect of Intermittent Theta Burst Stimulation Parameters on Biceps Corticomotor Excitability

Majdic, B.C. [1], Mittal, N. [1], Peterson, C.L. [1]
[1] Virginia Commonwealth University

Introduction: Neuromodulation as an adjuvant to physical rehabilitation may improve motor outcomes because increased excitability of muscle is associated with motor learning and skill acquisition. Intermittent theta burst stimulation (iTBS) is a non-invasive brain stimulation technique that can increase excitability of the corticospinal motor system (corticomotor excitability) [1]. Our long-term goal is to determine whether iTBS improves motor re-education after tendon or nerve transfer in individuals with tetraplegia and thereby increase activity gains following surgery. However, the efficacy of iTBS to increase excitability of the corticomotor pathway to proximal muscle (e.g., the biceps), muscle affected by spinal cord injury, or transferred muscle is unknown. As a first step, the purpose of our on-going study is to determine the effect of iTBS parameters (e.g., frequency and intensity) on corticomotor excitability of the biceps in nonimpaired individuals.

Materials and Methods: Subjects were instrumented with surface electromyography electrodes on their dominant arm biceps and triceps. Active motor threshold (AMT) was determined through the recording of motor evoked potentials (MEPs) in response to single pulse transcranial magnetic stimulation. Fifteen biceps MEPs at 110% of AMT, our measure of corticomotor excitability, were recorded before and 10, 20, and 30 minutes following sham and active iTBS. Parameters of iTBS delivered using a Magstim Super Rapid Plus stimulator consisted of three pulses presented at 30 Hz, repeated every 200 ms for 2 s at an intensity of 80% AMT. Two second bursts were repeated every 8 s for a total of 600 pulses.[14] For the sham condition, we used a sham coil (Magstim 70mm double air film sham coil), looking identical to the active coil (70mm double air film) and making a similar noise but without delivering any active stimulation. Two nonimpaired subjects participated in four sessions; each session was separated by one day to limit carry-over effects. Peak-to-peak MEP amplitudes were calculated; the difference in post- and pre-iTBS MEPs were normalized by the amplitude of the average MEP pre-iTBS stimulation and averaged across subjects and sessions.

Results and Discussion: The average decrease in normalized MEPs (± one standard deviation) recorded in the biceps following either active or sham iTBS at each 10 minute interval are shown in Figure 1. In our subjects to date, there was no difference in the active and sham conditions. While the goal of active iTBS is to increase corticomotor excitability, our results suggest iTBS at a frequency greater than 30 Hz is likely required. The AMTs in our participants were higher relative to previous iTBS studies targeting the flexor digitorum interosseous [2]. Due to limitations of our iTBS devices with regard to intensity and frequency output to minimize the risk of over-heating the coil, the maximum frequency at which stimuli could be delivered to maintain 80% AMT intensity was 30 Hz.

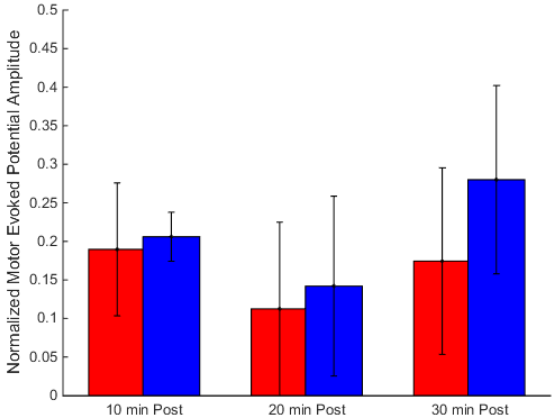

Figure 1. No differences in normalized biceps MEP amplitudes were observed between active (red) and sham (blue) iTBS delivered at 30 Hz.

Conclusions: Intermittent theta burst stimulation at 30 Hz frequency may not affect corticomotor excitability of the biceps in nonimpaired individuals. Future work will investigate the effect of decreasing stimulus intensity on biceps corticomotor excitability, while delivering iTBS stimuli at 50 Hz frequency.

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References: [1] Huang YZ, et al.. *Neuron* 2005;45(2):201-206. [2] Suppa A, et al. *Brain Stimulation* 2016 9: 323–335.

THE EFFECT OF INTERMITTENT THETA BURST STIMULATION ON BICEPS CORTICOMOTOR EXCITABILITY IN NONIMPAIRED INDIVIDUALS AND INDIVIDUALS WITH TETRAPLEGIA

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INTRODUCTION

Neuromodulation of the primary motor cortex (M1) in pair with physical therapy is a promising method for improving motor outcomes. Rationale for neuromodulation to target excitability of the corticospinal motor pathways (i.e., corticomotor excitability) is that increases in corticomotor excitability of upper limb muscles have shown to be associated with motor learning and skill acquisition [1-3]. Intermittent theta burst stimulation (iTBS) is a form of non-invasive brain stimulation which can increase corticomotor excitability and is advantageous over other forms of neuromodulation due to its short duration and low stimulation intensity [4].

The long-term goal of our study is to determine if iTBS paired with physical therapy can improve motor re-education of upper limb muscles after tendon or nerve transfer in individuals with tetraplegia. More proximal upper limb muscles, such as the biceps, can be surgically transferred to restore elbow extension. However, the ability for iTBS to increase the corticomotor excitability of proximal muscles such as the biceps brachii is currently unclear. The majority of studies involving iTBS have targeted the first dorsal interosseous (FDI) in non-impaired individuals. This is likely because the FDI is an easier target due to a high density of corticospinal neurons projecting to the muscle. These studies have found that iTBS can increase the amplitude of motor evoked potentials (MEPs) in non-impaired individuals for up to 30 minutes, however the effects often vary across participants resulting in negative findings group-wide. These results may differ in more proximal muscles, such as the biceps, due to differences in corticospinal control across flexors and extensors. One study which targeted the flexor carpi radialis (FCR), a muscle more proximal than the FDI, found that differences in the resting motor thresholds (RMT) between the FCR and its antagonist muscle (extensor carpi radialis) appeared to determine the efficacy of iTBS [5].

The purpose of this on-going study is to determine the effect of iTBS on the corticomotor excitability of the biceps, as measured by MEP amplitudes, in non-impaired individuals and individuals with tetraplegia. We hypothesize that iTBS will increase biceps MEP magnitude in non-impaired (NI) participants as well as persons with spinal cord injury (SCI). Furthermore, we hypothesize that the difference in RMT of the target and antagonist muscles (biceps and triceps respectively, RMT_T and RMT_A) will correlate with changes in MEP amplitude pre- and post-iTBS.

METHODS

Eight non-impaired individuals and four individuals with a low cervical (i.e., C5-C8) SCI have participated in this on-going study. Each participant completed three sessions of the protocol involving both active and sham iTBS, with each session separated by a minimum of three days in order to minimize the potential for carry over effects.
In each session, participants were instrumented with surface electromyography electrodes on the biceps and triceps of their dominant arm. The maximal compound muscle action potential (Mmax) was recorded from the biceps and triceps by delivering single pulse electrical stimuli to Erb's point via a bipolar stimulating electrode connected to a constant current stimulator (DS7AH, Digitimer Ltd.). Resting motor threshold (RMT) and active motor threshold (AMT) were then determined for the target muscle (biceps) by delivering single pulse transcranial magnetic stimulation (TMS) to the cortical area projecting to the biceps. RMT was also determined for the antagonist muscle (triceps). Single pulse TMS was delivered using a Super Rapid Plus stimulator (Magstim) via a 70 mm figure-of-eight coil. RMT was determined as the lowest stimulus intensity that induced MEPs of ≥ 50 μV in at least 5 of 10 consecutive stimuli with the target muscle fully relaxed. AMT was determined through the use

of an adaptive PEST software, developed by Borckardt et al., during sustained contractions of 10 ± 5% of the participant's maximum effort [6].

Fifteen biceps MEPs were recorded via single pulse TMS delivered at an intensity of 120% of RMT, at intervals 10, 20, and 30 min after sham and active iTBS. The iTBS parameters consisted of three pulses presented at 50 Hz, repeated every 200 ms for 2 s at an intensity of 80% of the participant's AMT. Two second bursts were repeated every 8 s for a total of 600 pulses [4]. iTBS was also delivered with the Super Rapid Plus stimulator. For the sham condition, a sham coil, looking identical to the active coil and making similar noise without delivering any active stimulation, was applied to the cortical area projecting to the biceps. Throughout each session, participants were kept unaware of the type of stimulation they were receiving.

Normalized MEPs (nMEP) were calculated as the MEP amplitude divided by the participant's average Mmax and averaged within each session separately for both active and sham coil in pre or post iTBS groups. A t-test was used to compare the change in nMEPs after iTBS between the active and sham coil data for both NI and SCI participant groups. Pearson's correlation was calculated for the difference between RMT_T and RMT_A, and nMEP post iTBS.

RESULTS

Magnitudes of nMEPs were increased after iTBS for the NI sham group, SCI sham group, and SCI active group ($p < 0.01$), but not NI active ($p = 0.40$). There was no difference between the post iTBS nMEP magnitudes between the active and sham coils in either group (NI $p = 0.52$, SCI $p = 0.15$). There were no correlations between post iTBS nMEP magnitude and RMT difference (1. sham coil NI; 2. active coil, NI; 3. sham coil, SCI; 4. active coil, SCI, respectively are: $r^2 = 0.014$, 0.014, 0.116, 0.176; all with $p > 0.05$). Mmax, RMT values, and MEP amplitudes are provided in Table 1.

Table 1: Average Mmax, resting motor thresholds (RMT) and MEP amplitudes for the NI group and SCI participants.

					pre-iTBS	post-iTBS
Subj	Session #	Mmax (mV)	RMT (Biceps)	RMT (Triceps)	MEP Amplitude (μV)	△ MEP Amplitude (μV)
Avg NI	1	3.96	89	100	17.7 ± 15	-2.45 ± 12
	2	3.37	91	100	11.1 ± 8.6	1.45 ± 8.7
	3	3.67	86	99	12.7 ± 10	2.18 ± 12
SCI 01	1	0.950	95	100	7.74 ± 5.1	1.21 ± 2.1
	2	0.151	92	100	8.73 ± 10	14.5 ± 19
	3	1.33	97	100	18.5 ± 5.6	-7.85 ± 3.4
SCI 02	1	7.70	82	100	7.90 ± 7.8	7.12 ± 5.9
	2	9.35	80	100	13.7 ± 6.2	26.9 ± 26
	3	9.68	88	100	11. 8 ± 11	7.05 ± 1.2
SCI 03	1	0.194	77	100	49.7 ± 15	-15.0 ± 5.2
	2	0.176	80	100	49.4 ± 19	-1.69 ± 11
	3	2.75	91	98	15.0 ± 16	18.3 ± 29
SCI 04	1	0.155	95	100	7.42 ± 3.9	-0.758 ± 2.2
	2	0.297	94	100	4.17 ± 1.9	0.456 ± 0.48
	3	1.03	97	100	12.1 ± 8.3	0.354 ± 2.21

DISCUSSION

We expected that iTBS would increase the corticomotor excitability of the biceps, represented by an increase in MEP amplitudes, in both NI and SCI participants. While there did tend to be an increase in MEP amplitudes post iTBS in both groups, our t-test showed that there was no significant difference in the change of nMEPs between sham and active protocols. Additionally, while we expected there to be a correlation between the RMT difference of the target and antagonist muscles and the changes in MEP amplitudes post iTBS for both groups, our Pearson's correlation tests showed that there were no correlations.

A key outcome of this study was that both groups had not only a high degree of inter-subject variability, but also a high degree of intra-subject variability in the measured change of biceps MEP amplitudes. This was evident as a result of evaluating MEPs across multiple sessions and utilizing a sham coil as a control. Similar research done with continuous TBS has also shown varying responses across multiple sessions for each individual [7]. In addition to the variable responses seen in studies targeting the FDI, there may be some benefit in investigating the effects of iTBS on each participant in each session, rather than a group-wide analysis approach. This is further supported by other work that found the effects of iTBS on the FDI were independent across multiple sessions [8].

RMT focused inferences are of limited value with this data, as RMT intensities were frequently near or above the maximum intensity available with our stimulation unit and coil. While the use of a single coil prevents us from stimulating at an intensity that could fully capture the magnitude of MEPs in participants with higher motor thresholds, it is more realistic for a clinical approach. To circumvent this shortcoming, other studies have used a separate simulation unit and coil to record RMT and MEPs [5].

The lack of a MEP facilitatory effect of iTBS could be driven by variables that this pilot study did not account for, such as genetic factors or baseline excitability. Furthermore, the effects of iTBS may be better observed using other modalities than MEP magnitude, such as EEG measurements or MEP latency, which have been used as alternative metrics [9,10]. Finally, as this is a presentation of preliminary findings, limited sample size is a current limitation of our work.

Our preliminary data suggests that on average there are no group-wide effects of iTBS on biceps corticomotor excitability in either the NI or SCI subject groups. This provides rationale for investigating effects of iTBS on an individual basis, and suggests further work is warranted to understand factors that contribute to inter-subject and intra-subject variability.

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The Effect of Intermittent Theta Burst Stimulation on Corticomotor Excitability of the Biceps and Transferred Muscles

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Summary

iTBS is being investigated as a method to promote motor re-education after an upper limb reconstruction surgery. We found iTBS to have a facilitory effect on corticomotor excitability in individuals with spinal cord injury and upper limb reconstruction. This suggests that iTBS may be a promising method for improving motor outcomes.

Introduction

Motor re-education of the muscles is critical for attaining optimal outcomes in individuals with spinal cord injury (SCI) who have had an upper limb reconstruction (ULR) surgery. Currently this re-education is achieved through physical therapy, however the strength and functional outcomes are variable and often substandard. Neuromodulation of the primary motor cortex (M1) in pair with physical therapy may be a promising method for improving motor re-education after a ULR surgery. Increases in the excitability of the corticospinal motor pathway (i.e. corticomotor excitability) projecting to upper limb muscles have shown to be associated with motor learning and skill acquisition [1-3]. Intermittent theta burst stimulation (iTBS) is a form of non-invasive brain stimulation which can increase corticomotor excitability. However, the ability for iTBS to increase the corticomotor excitability of proximal muscles such as the biceps brachii, muscles affected by SCI, or transferred muscles is currently unknown. Thus, the purpose of this on-going study is to determine the effect of iTBS on the corticomotor excitability of the biceps and transferred muscles, as measured by motor evoked potential (MEP) amplitudes, in non-impaired (NI) individuals, individuals with tetraplegia, and individuals who have had an ULR surgery.

Methods

Fifteen individuals have participated in this on-going study (10 NI, 4 SCI, 1 ULR). Participants completed three sessions of the protocol, each including sham and active iTBS. Sessions were separated by a minimum of three days to prevent the potential for carry over effects. NI and SCI participants were instrumented with surface electromyography electrodes on the biceps and triceps of their dominant arm, while ULR participants had them instrumented on their transferred muscle and its primary antagonist. The maximal compound action potential (Mmax) was recorded from these muscles for the normalization of MEPs (nMEP). Resting motor threshold (RMT) and active motor threshold (AMT) were then determined by delivering single pulse TMS using a Super Rapid Plus stimulator (Magstim) via a 70 mm figure-of-eight coil. Fifteen MEPs were recorded via single pulse TMS delivered at an intensity of 120% RMT, at intervals before, 10, 20, and 30 min after sham and active iTBS. The iTBS parameters consisted of three pulses presented at 50 Hz, repeated every 200 ms for 2 s at an intensity of 80% of the participant's AMT. Two second bursts were repeated every 8 s for a total of 600 pulses [4]. iTBS was also delivered with the Super Rapid Plus stimulator.

Results and Discussion

Change in MEP amplitude after iTBS was not different between sham and active coils in the NI group, but MEP amplitude was increased after active iTBS to a greater degree compared to sham in the SCI and ULR groups ($p = 0.45$, $p < 0.001$, $p < 0.001$). Mean values for each condition are found in Table 1.

Table 1: Average change in log transformed nMEP amplitude between pre- and post-iTBS, for NI, SCI, and ULR groups

Group	*NI*	*SCI*	*ULR*
Sham	0.102 ± 0.93	-0.317 ± 1.8	-0.342 ± 0.68
Active	0.0742 ± 0.96	0.305 ± 1.9	0.509 ± 0.92

Active and sham iTBS had no effect in NI participants which is consistent with both continuous TBS work in the biceps and iTBS studies in the FDI in NI individuals [5,6]. Meanwhile, active iTBS was found to have a facilitory effect on the biceps and transferred muscles of SCI and ULR participants. This is consistent with findings in iTBS of the FDI in individuals with SCI [6,7]. Currently, data for SCI and ULR subjects is preliminary and testing is ongoing.

Conclusions

iTBS of the biceps has variable effects on corticomotor excitability in NI individuals but is excitatory in those with SCI and ULR.

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Vita

Blaize Majdic was born July 29th, 1994 in Wilkes Barre, Pennsylvania and grew up in Williamsburg, Virginia. He graduated from Jamestown High School in 2012 and went on to attend James Madison University to pursue a bachelor's degree in engineering. During his undergraduate studies, Blaize led projects in developing novel prosthetic systems for transtibial amputees and researching cognitive functions through the use of EEG. In his spare time, Blaize volunteered for and was a member of JMU SafeRides where he served as a team leader and director for the organization. He also served as a first-year orientation guide to welcome incoming students and guide them through their first year at JMU. After graduating in spring 2017, Blaize began attending Virginia Commonwealth University in the fall as a master student pursuing a degree in biomedical engineering. He joined the Rehabilitation Engineering to Advance Ability Lab (REALab) under Dr. Carrie Peterson to study the effect of non-invasive brain stimulation on motor function after spinal cord injury. While completing his graduate degree and research, Blaize worked part time at VCU's Innovation Gateway as a licensing liaison to help foster the development of VCU inventions. He hopes to use these experiences in the future to aid him in developing innovative devices for rehabilitation.