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Control of Ankle Dorsiflexion in Persons with Spinal Cord Injury: Neurophysiology and Neuromodulation via Afferent Stimulation

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Abstract

Control of Ankle Dorsiflexion in Persons with Spinal Cord Injury: Neurophysiology and Neuromodulation via Afferent Stimulation

By Jasmine Marie Hope

Diminished ankle control impedes walking ability in persons with spinal cord injury (SCI). Although some neurological mechanisms of this deficit are known in other populations, there is limited evidence of the pathophysiology of SCI as it relates to both dorsiflexor volitional activation and plantar-flexor spasticity. Furthermore, as noninvasive afferent stimulation therapies are increasingly utilized in rehabilitative therapy, it is important to understand how to optimize these tools to address diminished ankle control. As ankle control is heavily influenced by corticospinal tract descending drive and spinal pattern-generating circuits in a task-dependent manner, the impact of neuromodulatory techniques must be examined across different tasks. Therefore the purpose of my dissertation was to 1) synthesize what is known about the neurophysiological mechanisms of dorsiflexor control after SCI, 2) utilize neuromodulatory techniques that target those mechanisms to determine their persistent impacts on dorsiflexor control, and 3) assess dorsiflexor control across different tasks to distinguish the role of these neurophysiological mechanisms in those tasks, in persons with SCI.

In Chapter 2, we synthesized what was known about the contribution of corticospinal tract descending drive and spinal reflex circuit modulation to disrupted ankle control. In Chapter 3, we determined if there were persistent effects of different doses of robust noninvasive afferent stimulation, in the form of whole body vibration, on dorsiflexion during swing phase of walking and plantar-flexor spinal reflex modulation. Finally, in Chapter 4, we examined the existence of a persistent impact of combined locomotor training and transcutaneous spinal stimulation on dorsiflexion during both the swing phase of walking and a volitional task in participants with SCI.

This dissertation has established 1) a relationship between neurophysiological measures with volitional ankle control and spasticity, 2) whole body vibration and transcutaneous spinal stimulation do not have a persistent impact on dorsiflexor control during walking or volitional activation, but locomotor training may have a persistent impact on these outcomes, and 3) corticospinal descending drive is important for dorsiflexor activation during walking in persons with SCI. The above findings are important steps toward the optimization of rehabilitative therapy in persons with diminished ankle control after SCI.

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Dedication

I dedicate this dissertation to my late Grandfather, Ernest Gaylord Bonner. I know he would have been happy to see me earn my PhD, I know he is always watching, and I hope he is proud.

I also would like to dedicate this to my wonderful Husband, James Hicks; my parents, Leila and Andrew Hope; my siblings Andrea, Matthew, and Armani Hope; my might as well be siblings Lana and Destin Hope; my aunt and uncle Tina and Ron Hope; my grandmothers Ernestine and Renee; and all my family near and far who have always been my biggest cheerleaders! And to my friends that supported me in the Neuroscience Program and beyond, my Hulse Lab family, and my community Mozley Park. For all the times I had to come to you to vent, cry, or laugh, thank you for listening, being there, and supporting me. I could not have done this without you, like, seriously. Thank you!

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Chapter 1: Control of dorsiflexor activation after SCI: neurophysiological mechanisms and neuromodulation of foot drop and ankle clonus.

STATEMENT OF THE PROBLEM: LACK OF DORSIFLEXOR CONTROL IN PERSONS WITH SCI

- *Control of dorsiflexors after motor incomplete SCI (foot drop)*

There are approximately 299,000 people in the United States living with spinal cord injury (SCI) (National Spinal Cord Injury Statistical Center, 2022). Of those people, 66.5% have incomplete injuries (National Spinal Cord Injury Statistical Center, 2022). People with motor-incomplete SCI have preserved motor function below their neurological level of injury, but are unable to move some key muscles against gravity (Burns et al., 2012). When this inability to move against gravity occurs in the muscles that control the ankle, it is known as foot drop (van der Salm et al., 2005). Foot drop can occur after upper motor neuron damage, and is characterized by inadequate dorsiflexion, especially during the swing phase of walking (Carolus et al., 2019). In a study with persons with motor-incomplete SCI, 76% of participants had excessive plantar-flexion, which impacted foot clearance during swing phase (van der Salm et al., 2005). Excessive plantar-flexion during swing phase of the gait cycle has been associated with the diminished ability to activate dorsiflexor muscles and is one characteristic of a phenomenon known as spastic gait pattern (Yang et al., 1991).

As a consequence of spastic gait pattern, walking function is impaired after SCI due to insufficient clearance of the foot during swing phase. Not only does foot drop impact the ability to safely ambulate by increasing fall risk (Kemoun et al., 2002), it also impacts the ability to safely transfer in and out of a wheelchair (Adams & Hicks, 2005) and decreases quality of life (Trgovcevic et al., 2014). Ankle foot orthotics have been used to treat the symptoms of foot drop by fixing the position of the ankle; however, the use of these devices can decrease balance control and create an abnormal gait pattern (Delafontaine et

al., 2017). There has also been an association between ankle foot orthotic use with decreased muscle strength (Geboers et al., 2002). Because regaining walking function is one of the top priorities after SCI (Anderson, 2004), it is important to develop interventions that can improve functional outcomes by modulating underlying neurophysiological mechanisms. As foot drop can be a consequence of upper motor neuron damage (Carolus et al., 2019), it not only impacts persons with SCI, but also people with stroke (Dobkin, 2005) and cerebral palsy (Hullin et al., 1996). Therefore, identifying techniques to improve functional outcomes for people with foot drop has broad implications.

To monitor how different interventions can impact foot drop, objective measurements can be quantified using motion capture. Motion capture can obtain measures such as toe elevation in reference to height of the foot from the ground and ankle excursion (Barthelemy et al., 2010). However, several factors contribute to toe elevation including knee or hip flexion angles (Barthelemy et al., 2010), and ankle excursion during swing phase can be biased by increased plantar-flexion at the initiation of swing (Barthelemy et al., 2010). In other populations in which diminished ankle control impairs walking, it is standard to measure peak dorsiflexion angle during swing phase (Kesar et al., 2011). Therefore, to allow for broader future implications of my present findings to other populations impacted by foot drop, and to provide more specificity about the role of the dorsiflexors during walking, in this dissertation, measurement of peak dorsiflexion angle during swing phase was captured.

- *Spasticity in the plantar-flexors after motor-incomplete SCI (ankle clonus)*

Similar to foot drop, spasticity can also develop after upper motor neuron damage (Adams & Hicks, 2005). The traditional definition of spasticity is limited to the velocity-dependent increase in muscle tone due to hyperreflexia in response to a stretch (Lance, 1980). However, during a subsequent consortium there was a proposal to create a more comprehensive definition of spasticity that includes all involuntary muscle activation whether intermittent or sustained as a result of upper motor neuron damage (Pandyan et al., 2005). There is a push within the field of neurorehabilitation to recognize the heterogenous presentation of spasticity in those impacted. In a recent survey of people with SCI who have spasticity,

spasticity occurred spontaneously without stretch to the muscle in some participants (Field-Fote et al., 2022). Furthermore, stiffness was reported to be the most problematic experience (Field-Fote et al., 2022). Therefore, for my dissertation spasticity is characterized by uncontrollable muscle movements associated with spasms, stiffness, and rhythmic oscillations of the muscles impacted. Different presentations of spasticity can have negative consequences on the ability to safely ambulate. For instance, spasticity can further hinder walking ability due to both rhythmic oscillations, stiffness, and hyperreflexia in the soleus, which all characterize spastic gait pattern (Adams & Hicks, 2005).

The inability to dorsiflex the ankle during swing phase observed in spastic gait pattern is in part due to hyperreflexia in the soleus muscle. In persons with spastic gait, when the soleus muscle is stretched at terminal stance, hyperreflexia causes a prolonged muscle contraction that carries over into swing phase (Knikou et al., 2009). Because of the reciprocal relationship between plantar-flexor and dorsiflexor muscles, a contraction in one muscle can lead to the inhibition of the other in people who are non-injured (Knikou, 2008). However, after SCI, this relationship can become facilitatory (Crone et al., 2003), further diminishing the appropriate control and timing of dorsiflexion during walking.

In some cases, spasticity in the soleus can lead to a phenomenon known as ankle clonus, wherein a stretch of the soleus muscle leads to rhythmic oscillations about the ankle joint (Manella et al., 2017). Ankle clonus is characterized by at least 4 repeated rhythmic movements about the ankle joint (Koelman et al., 1993) at a frequency of 4-9Hz (Beres-Jones et al., 2003). Analogous to foot drop, this phenomenon also occurs in groups outside of individuals with SCI, including persons with stroke (Li & Francisco, 2015). There are several ways to measure ankle clonus. In clinical settings, the spinal cord injury assessment tool for spastic reflexes (SCATS) has been used to quantify the duration of spasticity, in which the reaction to a quick stretch of the plantar-flexors is scored on a 4- point scale based on duration of the clonus (0, no reaction; 1, mild/ less than 3 seconds; 2, moderate/3-10 seconds; 3, severe/ at least 10 seconds) (Benz et al., 2005). To assess ankle clonus severity more objectively, a standardized mechanical perturbation known as the drop test can be used (Manella et al., 2017). In our lab group, we validated the SCATS against the drop test. We determined that not only are these outcomes comparable, but that the

drop test allows for additional measurements including plantar-flexor reflex threshold (Manella & Field-Fote, 2013), number of oscillations, and duration of oscillations (Manella et al., 2017).

WHAT WE KNOW: NEUROPHYSIOLOGICAL MECHANISMS OF DORSIFLEXOR CONTROL

- *Corticospinal tract decreased descending drive to tibialis anterior leads to foot drop*

Initiating voluntary control of the distal muscles requires the excitation of pyramidal neurons in the primary motor cortex which descend to lower motor neurons in the spinal cord (Fromm & Evarts, 1982). This pathway is known as the pyramidal or corticospinal tract (CST). The CST has a strong connection with the tibialis anterior muscles responsible for dorsiflexion of the ankle (Capaday et al., 1999). Furthermore, there is evidence that tibialis anterior activation is more highly dependent on CST descending drive than any other lower extremity muscle (Capaday et al., 1999; Schubert et al., 1997). Unsurprisingly, damage to the CST can greatly impact the dorsiflexor muscles and is related to foot drop (Barthelemy et al., 2010).

Foot drop in people with SCI and other populations has been directly linked to CST descending drive in studies that utilize transcranial magnetic stimulation (TMS) (Barthelemy et al., 2013; Barthelemy et al., 2015; Barthelemy et al., 2010). Using this tool, experimenters can elicit a motor evoked potential (MEP) by targeting the primary motor cortex area which controls the muscle of interest and assess the strength of CST descending drive via recording electrodes placed on that muscle (Levy, 1987). In one such study, foot drop, as measured by maximum toe elevation, was associated with impaired CST transmission to the tibialis anterior (Barthelemy et al., 2013). There is also evidence of a general relationship between enhanced functional magnetic resonance imaging signals during a dorsiflexion task and improved walking function in persons with stroke (Dobkin et al., 2004). Furthermore, connections have been made between CST transmission, foot drop, and walking function in persons with SCI. For example, MEP amplitude at rest has a strong positive correlation with toe elevation and overground walking speed (Barthelemy et al.,

2013).

The CST not only has direct excitatory synapses onto lower motor neurons, but also innervates inhibitory interneurons that modulate the spinal reflex circuit (SRC) (Smith & Knikou, 2016). This important connection provides a check and balance for the SRC. Although reflexes are thought to be involuntary, they can be altered through input from supraspinal excitatory signals (Meunier & Pierrot-Deseilligny, 1998). Therefore, a decrease in excitatory input onto inhibitory interneurons can lead to a net increase in excitation. Additionally, the decrease in direct descending input onto lower-motor neurons can also have negative consequences. For instance, after upper motor neuron damage, there is an increase in the expression of constitutively active serotonin receptors in response to the decreased supraspinal-derived serotonin on the lower motor neurons (Murray et al., 2010). These direct and indirect consequences of upper motor neuron damage are thought to be some of the mechanisms behind the development of spasticity (Murray et al., 2010).

- *Spinal reflex circuit lack of inhibition to soleus is associated with spasticity*

The control of the dorsiflexor muscles is not only dependent on corticospinal drive, but also a balanced SRC. The monosynaptic spinal stretch reflex encompasses IA muscle spindle fiber activation in response to stretch followed by direct activation of the alpha- motoneuron back onto the muscle, resulting in a contraction (Burke et al., 1983). To objectively measure the spinal stretch reflex, a non-invasive electrical stimulation technique was developed known as the Hoffmann (H)- reflex (Knikou, 2008). The H-reflex bypasses the muscle spindle by directly stimulating the IA afferents (Schieppati, 1987). There are several measures that can be assessed from this stimulation, including H/M ratio, reciprocal inhibition, and presynaptic inhibition (Knikou, 2008).

There is evidence that the monosynaptic spinal stretch reflex is altered during walking in a phase-dependent manner. For instance, in persons without neurological injury, the soleus SRC is in a more excited state during stance phase but depressed during swing phase in response to stimulation of the IA afferent fibers (Knikou et al., 2009). After SCI, the depression of the soleus H-reflex, was diminished

during swing phase (Knikou et al., 2009), thus suggesting that the SRC is in a hyperexcitable state. This pathophysiological change in the H-reflex depression after SCI has been associated with plantar-flexor hyperexcitability at terminal stance into swing phase in other populations (Berger et al., 1988). Thus, the increased excitability of the monosynaptic spinal stretch reflex in the soleus may result in in foot drop.

Plantar-flexor spasticity can further diminish the ability to dorsiflex the ankles in a controlled manner, due to the pathophysiological changes that underly the relationship between plantar-flexors and dorsiflexors after SCI. In non-injured individuals, activation of the tibialis anterior results in excitation of the IA inhibitory interneuron which then inhibits the activation of the soleus and vice versa (Petersen et al., 1999). After SCI, there is evidence that reciprocal inhibition can become reciprocal facilitation (Mirbagheri et al., 2014). In fact, in people with spasticity after incomplete spinal cord injury, impaired reciprocal inhibition was associated with antagonist coactivation (Boorman et al., 1996). Thus, during dorsiflexor muscle contractions, there is increased activation of soleus muscles, decreasing the ability to selectively activate the muscle of interest.

Another alteration in the SRC after SCI can be observed by measuring presynaptic inhibition. Due to the diminished supraspinal input onto inhibitory interneurons, there is a decrease in presynaptic inhibition of the SRC (Smith & Knikou, 2016). One useful tool to assess modulation of presynaptic inhibition is low frequency depression (LFD) (Calancie et al., 1993; Field-Fote et al., 2006), in which the IA afferents are stimulated multiple times at a set time interval. In our lab group, we use an inter-stimulus interval of 1Hz, as this is the frequency at which LFD is reported to be the most robust (Knikou, 2008). After SCI and stroke, diminished LFD has been associated with increased spasticity (Masakado et al., 2005; Smith & Knikou, 2016).

There are several underlying neurological changes that contribute to the hyperexcitable state of the monosynaptic stretch reflex. One such change that occurs after SCI is the alteration in the effect of gamma aminobutyric acid (GABA) on postsynaptic inhibition. In non-injured individuals, GABA has an inhibitory effect due to the extracellular concentration of chloride (Cl^-) being greater than intracellular concentrations (Ben-Ari, 2002). Thus when the GABA- A receptor is activated by GABA, there is a net

negative charge as Cl^- enters the cell. After SCI, the intracellular Cl^-concentration gradient reverses, and the intracellular Cl^- concentration is greater than the extracellular concentration (Ben-Ari et al., 2012). This results in a net positive intracellular charge as Cl^- leaves the cell when GABA activates its receptor (Cramer et al., 2008). The change in Cl^- concentration gradient after SCI has been associated with a decrease in potassium- chloride cotransporter 2 (KCC2), which functions to pump Cl^- extracellularly to maintain the appropriate gradient (Ben-Ari et al., 2012). There has been evidence that exercise can modulate Cl^- homeostasis toward pre-injury levels by upregulating KCC2 (Cote et al., 2014). To reverse the negative consequences of spasticity, it will be important to utilize tools that target the above neurophysiological mechanisms.

- *Locomotor central pattern generator's role in dorsiflexion during swing phase*

In addition to the control of dorsiflexion being influenced by CST descending drive and SRC excitability, the locomotor central pattern generator (CPG) also plays a key role. The CPG is a neuronal circuit that generates rhythmic activation in a reciprocal feedforward manner in the absence of supraspinal control (Minassian et al., 2017). In decerebrated cat models, step-like behavior was observed when cats were placed on a treadmill (Gerasimenko et al., 2005). Therefore, it has been hypothesized that the locomotor CPG is responsible for the rhythmic motor pattern observed in the lower extremity muscles during walking. However, the existence of the locomotor CPG in humans is still a matter of debate due to the limited locomotor recovery after upper motor neuron damage (Minassian et al., 2017).

In persons with incomplete SCI, spontaneous activity has been observed in a flexor-extensor and left-right pattern-generating manner, however, when those same participants were asked to generate the step-like movement voluntarily, they were not able to do so (Calancie, 2006). Similar observations of spontaneous rhythmic, but not patterned, activity were also witnessed in persons with complete injuries (Calancie, 2006). When applying vibration to the thigh muscles, both persons with complete and incomplete SCI produced step-like behavior (Field-Fote et al., 2012). Therefore, there is evidence of the existence of locomotor CPG in humans that influence the generation of lower extremity muscle activation

(Knikou, 2010; Minassian et al., 2017).

Although dorsiflexor volitional activation during an isolated single-joint movement and dorsiflexor activation during walking are both influenced by CST descending drive (Capaday et al., 1999), the latter movement is also dependent on the locomotor CPG (Calancie et al., 1994). Additionally, although the CPG does not require input from supraspinal centers, there is evidence that the CST can impact the CPG (Minassian et al., 2017) . To distinguish the role of CST and CPG on control of ankle dorsiflexors, it is important to measure dorsiflexor activation across both volitional activation tasks and during walking. For instance, in persons who undergo locomotor training, it would be predicted that dorsiflexion during swing phase would improve more than dorsiflexion during a volitional task. This is because of both the specificity of the training (Hubbard et al., 2009) and the involvement of the CPG in the activation of dorsiflexion during swing phase (Calancie et al., 1994). Conversely, if similarities in dorsiflexion were observed during both the swing phase of walking and during a volitional task after the task-specific practice of locomotor training, this would suggest that other neurophysiological mechanisms, such as CST descending drive, play a more predominant role in the control of ankle dorsiflexors. For example, increasing cortical drive can improve walking outcomes after SCI (Bonizzato & Martinez, 2021; Hu et al., 2021). Therefore, improvements in dorsiflexion during swing phase may be more reflected in changes in CST descending drive and not necessarily altered CPG. Or perhaps these outcomes are influenced by altered reflex feedback due to SRC modulation after injury.

ADDRESSING THE PROBLEM: NONINVASIVE AFFERENT STIMULATION TO PROMOTE NEUROMODULATION

- *Whole body vibration increases supraspinal descending drive and decreases hyperactivation of spinal reflex circuit*

To combat functional and spasticity-related consequences of SCI, interventions have been developed to target the neurophysiological mechanisms underlying the pathophysiology of SCI (Field-Fote, 2015).

One such technique is robust afferent stimulation, which targets the proprioceptors and modulates CST descending drive and SRC excitability (Krause et al., 2016). Whole body vibration (WBV) is a noninvasive form of robust afferent stimulation that is utilized in rehabilitation settings. Most WBV platforms provide vibration in a sinusoidal vertical pattern and allow for customization of the frequency and amplitude of the vibration applied.

There is evidence that WBV can improve functional outcomes (Ness & Field-Fote, 2009b) and decrease spasticity (Ness & Field-Fote, 2009a). To further enhance these outcomes, our lab group has studied the dose-response (frequency, amplitude, and number of bouts) effects of WBV. To date, we have found evidence that 8 bouts of high frequency (50Hz) WBV decreased quadriceps spasticity up to 45 minutes post intervention, in comparison to 4 bouts at a lower frequency (30 Hz) in people with SCI and a high level of spasticity (Estes et al., 2018). In another study, 50Hz WBV frequency was associated with improved quadricep strength (Bosveld & Field-Fote, 2015) and improved walking speed (Ness & Field-Fote, 2009b) in individuals with SCI. Since there has been evidence that multiple sessions WBV resulted in a persistent decrease in quadricep spasticity up to 6-8 days after WBV (Ness & Field-Fote, 2009a), we predict that there will be a persistent impact of multiple sessions of 50 Hz WBV on dorsiflexion during swing phase of walking and hyperreflexia in the plantar-flexors.

- *Transcutaneous spinal stimulation increases volitional ankle control and improves walking and spasticity outcomes*

  Transcutaneous spinal stimulation (TSS) is a form of noninvasive afferent stimulation which utilizes cathodal-stimulating electrodes placed on the skin overlaying the spinous processes to activate posterior root nerve fibers (Hofstoetter et al., 2018). TSS has been associated with improved functional outcomes (Hofstoetter et al., 2015) and decreased spasticity (Hofstoetter et al., 2014). Like WBV, these changes are associated with different frequencies of stimulation. For instance, 30 Hz TSS has been associated with increased walking speed (Hofstoetter et al., 2015), while 50 Hz TSS has been associated with decreased spasticity (Sandler et al., 2021) in people with SCI. There is also

evidence that 30 Hz TSS has an immediate impact on dorsiflexor activation in persons with incomplete SCI (Meyer et al., 2020). Although, some studies demonstrate that 50 Hz TSS can also impact walking outcomes (Estes et al., 2021). The effects of 50 Hz TSS has been shown to have a temporal persistence on walking speed and spasticity 2- and 24 hours post stimulation respectively (Hofstoetter et al., 2021). However those results were from a study in persons with multiple sclerosis. Therefore in this dissertation, the impact of 50 Hz TSS on dorsiflexor control and plantar-flexor spasticity was assessed. As there is a push to use TSS as an adjunct to rehabilitative therapy, it is important to understand the timing of the effects. Therefore, one of the goals of my dissertation was to assess the temporal persistence of 50 Hz TSS on dorsiflexor control in persons with SCI.

- *Locomotor training in conjunction with noninvasive afferent stimulation further improves outcomes compared to locomotor training alone*

Exercise has been an important approach to improving outcomes in persons with upper motor neuron damage. In fact, exercise has been associated with improved gait deficits (Moore et al., 2010) and decreased spasticity (Fujimoto et al., 2021). These benefits have even been observed at the cellular level in persons with SCI, with restoration of the Cl^- equilibrium potential after exercise (Cote et al., 2014). Although strength and cardiovascular training are important, there is strong evidence supporting the advantages of task-based practice in rehabilitative therapy (Hubbard et al., 2009). For instance, to improve over-ground walking, it is best for a locomotor training program to include over-ground walking practice.

Unfortunately, most people do not receive the number of repetitions necessary to achieve their desired therapy goals after SCI (Sandler et al., 2017). Therefore, non-invasive stimulation has been used as a primer or adjunct to therapy to increase the likelihood of improved outcomes (Field-Fote, 2015). In a previous pragmatic study from our lab group, the addition of TSS to locomotor training improved walking outcomes more than locomotor training alone (Estes et al., 2021). Therefore, in this dissertation, I predict that TSS in combination with locomotor training will improve dorsiflexion

during walking in comparison to locomotor training alone.

FILLING THE GAPS IN KNOWLEDGE: DISSERTATION

To address the problem of lack of dorsiflexor control in persons with SCI, we must first establish evidence for a relationship between the neurophysiological mechanisms of CST descending drive and SRC excitability in regard to volitional control of the dorsiflexors and plantar-flexor spasticity. A better understanding of the underlying neurophysiological mechanisms of ankle control will set the foundation for optimization of noninvasive afferent stimulation to increase dorsiflexor control, decrease plantar-flexor spasticity, or both. Once this is established, we will further this knowledge by utilizing different forms of noninvasive afferent stimulation and determine its persistent impact on dorsiflexor activation across different tasks as well as measures of plantar-flexor spasticity and spinal reflex excitability. Therefore, the purpose of my dissertation is to: 1) gather what is known about the neurophysiological mechanisms of dorsiflexor control after SCI, 2) utilize neuromodulatory techniques that target those mechanisms to determine the persistent impact of these techniques on dorsiflexor control, and 3) assess dorsiflexor control across different tasks to distinguish the role of these neurophysiological mechanisms in persons with SCI.

- *Question 1: What is the relationship between corticospinal descending drive and spinal reflex circuitry with control of dorsiflexors and plantar-flexor spasticity?*

Specific Aim: Synthesize what is known about how changes in corticospinal transmission and spinal reflex excitability contribute to disrupted ankle control after SCI.

In Chapter 2, I conducted a scoping review to assess the relationship between CST descending drive

and SRC modulation on the functional and spasticity-related outcomes observed after SCI. The overall goal of this study was to distinguish the mechanisms of functional and spasticity-related measures on ankle control in persons with SCI. I hypothesized that there would be an association between disrupted corticospinal transmission and modulated spinal reflex excitability with diminished ankle control after SCI. Gaining this understanding is significant because it sets the necessary foundation to begin utilizing existing interventions that will target the underlying neurophysiology of ankle-related pathophysiology.

- *Question 2: Does robust afferent stimulation impact dorsiflexion during swing phase and spinal reflex excitability?*

Specific Aim: Determine the impact of whole body vibration on dorsiflexion during swing phase and spinal reflex circuit excitability.

In Chapter 3, I built upon previous evidence of the persistent effect of multiple sessions of WBV on walking outcomes to assess if these improvements were due to improved ankle control. Furthermore, because of the relationship between plantar-flexor spasticity and dorsiflexor control, I predicted that improvements observed after WBV may be related to soleus SRC modulation. Therefore I hypothesized that there would be a persistent impact of WBV on increased dorsiflexion during swing phase and decreased SRC excitability, in a dose-dependent manner.

- *Question 3: Is there a persistent effect of combined locomotor training and transcutaneous spinal stimulation on dorsiflexion across tasks in persons with spasticity?*

Specific Aim: Determine the persistent impact of combined locomotor training and transcutaneous spinal stimulation on volitional ankle control during a volitional task and walking in persons with

SCI.

Since TSS impacts both walking and ankle control measures, I predicted that improvements previously observed in walking outcomes were related to improved dorsiflexor control in Chapter 4. In this study, locomotor training combined with 50 Hz TSS was predicted to improve dorsiflexor control during both walking and a volitional activation task. Furthermore, I predicted that improvements in dorsiflexion during swing phase would be higher compared to dorsiflexor control during a volitional task due to both the role of CPG in walking and the incorporation of locomotor training into the intervention. Therefore, I hypothesized that locomotor training combined with transcutaneous spinal stimulation would have a persistent effect on dorsiflexion during walking and dorsiflexor active range of motion beyond that observed with locomotor training alone and that dorsiflexion during walking would show greater improvements than dorsiflexion during the volitional task, due to role of CPG in walking and because LT was utilized in this study.

Chapter 2: Disrupted ankle control and spasticity in persons with spinal cord injury: the association between neurophysiologic measures and function. A scoping review

1. Introduction:

Walking is a high-priority goal for most persons with spinal cord injury (SCI) (Ditunno et al., 2008). For walking to be the primary means of mobility, several conditions must be satisfied including low energy expenditure, good safety, and adequate speed for practical community-based walking (van Hedel & Group, 2009) . Each of these conditions is highly dependent on a number of factors, including the degree of control present at the ankle (Dubin, 2014). Likewise, ankle control is influenced by a multitude of interrelated factors such as muscle strength, timing of activation, and spasticity, which collectively determine gait mechanics (Barbeau et al., 2006; Dobkin et al., 2004; Manella et al., 2017). Without adequate ankle dorsiflexion, foot drop during the swing phase of gait can impair foot clearance, contribute to decreased stride length, and increase likelihood of falls (Varoqui et al., 2014). Secondary gait deviations often develop to achieve foot clearance, including excessive hip and knee flexion, limb circumduction, or lateral trunk sway with pelvic hike. These deviations increase the energy cost of walking and decrease the likelihood that walking is a safe and feasible means of mobility (Dubin, 2014).

Ankle-related impairments after SCI are attributed to neurophysiologic changes in both corticospinal tract (CST) transmission (Barthelemy et al., 2010) and modulation of spinal reflex circuit (SRC) excitability (Knikou, 2010) (**Figure 2.1**). To better understand the influences of CST transmission and SRC excitability, two commonly performed electrophysiological measures are utilized: cortical motor evoked potentials (MEPs) and Hoffman reflex (H-reflex). Both measures are commonly used as non-invasive probes of the underlying neurophysiology of CST transmission and SRC excitability, respectively. Decreased descending transmission impairs volitional control of the dorsiflexors (DF) as well as reduces inhibition to the plantar flexors (PF), further contributing to aberrant SRC activity. It is important to note that while the H-reflex is commonly used as a measure of excitability of the monosynaptic IA SRCs, this reflex measure reflects oligosynaptic inputs(Burke et al., 1983).

Some study findings suggest that the reorganization of the cortical motor representation after SCI results in decreased volitional drive through the spared spinal pathways. Evidence indicates that training and neuromodulation approaches directed at increasing volitional drive can increase the amplitude of MEPs (Norton & Gorassini, 2006; Thomas & Gorassini, 2005), restore normal cortical organization (Hoffman & Field-Fote, 2013; Hoffman & Field-Fote, 2007), and improve volitional muscle activation (Gomes-Osman et al., 2016; Manella et al., 2013). Altered activity of SRC, due to reorganization of spinal circuits and disruption of normal SRC modulation from descending corticospinal input, can result in several signs and symptoms commonly associated with spasticity after SCI. These symptoms include clonus or hyper-reflexive response to afferent input (i.e. stretch, touch, cold temperatures), muscle stiffness (hypertonia), and spontaneous involuntary muscle contractions (spasms) (Adams & Hicks, 2005; McKay et al., 2018). The maladaptive changes to the circuits controlling the DF and PF following SCI have been described (Boulenguez et al., 2010; Gorassini et al., 2004; Smith & Knikou, 2016); however, the relationship between decreased CST descending drive and disrupted SRC modulation with volitional ankle control (VAC) (dorsiflexion during gait, toe tapping, etc.) and/or spasticity remains unclear.

In order to improve functional outcomes after SCI, several recent advances have focused on neuromodulation of the corticospinal and spinal circuits. These advances have been summarized in a recent review (James et al., 2018), and include non-invasive stimulation of afferent inputs such as peripheral nerve somatosensory stimulation, whole body vibration, and transcutaneous spinal cord stimulation. These modalities directly modulate SRC excitability and indirectly activate corticomotor circuits (Field-Fote, 2015). There are also techniques that directly target increased CST descending drive such as transcranial direct current stimulation and repetitive TMS (Field-Fote et al., 2017). All of these neuromodulatory approaches have been shown to improve functional outcomes, including walking function, when used as an adjuvant to therapy (Field-Fote, 2015). Although these advances show promise for improving walking, to truly optimize functional outcomes it is necessary to understand how

neuromodulation of the CST and the SRCs impact variables that are elemental to walking function, such as ankle control and spasticity. As a precursor to exploring the impact of neuromodulation, a better understanding of how neurophysiological measures are related to VAC and spasticity is needed.

To elucidate the respective roles of CST transmission and SRC excitability in disrupted ankle control, we conducted a scoping review to summarize what is known and to identify existing gaps in the literature in order to frame more precise questions for future studies (Peters et al., 2015). The objectives were to (1) summarize state of the literature (study designs, methods, evidence of an association), (2) identify existing gaps (variability, contradictions, lack of evidence), and (3) propose future directions (based on existing gaps). Addressing these objectives is important to understand the relationship between corticospinal and spinal neurophysiological measures in the DF and PF and their association with ankle-related function. A better understanding of this association will (1) facilitate the development of more targeted therapeutic strategies for improving ankle control, (2) refine spasticity management, and (3) enhance quality of life for persons with SCI.

2. Materials and Methods

In the current review, we used the five stages of a scoping review outlined by Arksey and O'Malley as a guide (Arksey & O'Malley, 2005): (1) identify the research question, (2) identify relevant studies, (3) select studies for inclusion, (4) [extract and] chart the data, and (5) collate, summarize, and report the results.

2.1 Inclusion/Exclusion Criteria

To determine the scope and extent of the literature, we used inclusion and exclusion criteria that focused on the association between neurophysiological measures and VAC and/or spasticity measures in persons with SCI. For inclusion, all studies had to include adults (mean age $\geq$ 18 years old) with SCI. Studies that compared measures obtained from persons with SCI to individuals with other neurological disorders or non-injured individuals were eligible for inclusion. Studies had to include the H-reflex and/or MEPs as measures of spinal and corticospinal neurophysiological changes, respectively. Peripheral nerve

stimulation to evoke H-reflexes and transcranial magnetic stimulation (TMS) to evoke MEPs have been shown to be repeatable and consistent in both the DF and PF muscles (Leung et al., 2018; Tallent et al., 2012). Studies had to include at least one of these approaches to be eligible for inclusion in the review. To address the relationship between neurophysiological excitability and ankle functional measures, studies had to include at least one measure of VAC (e.g. ankle strength, ankle tapping, foot drop/toe drag during walking) and/or ankle spasticity (e.g. ankle clonus, ankle stiffness). Studies were excluded if subjects who lacked volitional ankle movement were enrolled or if ankle-specific results were not reported. Only studies published in English were included. Case studies, non-peer reviewed sources (e.g. dissertations, conference abstracts, unpublished data), theoretical simulations or models, and reviews were also excluded from the final review.

2.2 Sources and Search

In consultation with a medical librarian, the following databases were searched for articles published between the time of database inception to April 2018: PubMed (includes MEDLINE), Ovid-Medline, and EBSCO-CINAHL. The search terms were chosen to capture articles that included persons with SCI, spinal or corticospinal neurophysiological testing, and functional testing of the ankle DF or PF. The details of the terms and search combinations are described in **Table 2.1**. To restrict the population of interest to SCI, the following search terms were always used in combination with the other terms across all databases: (Spinal Cord Injury [Title/Abstract] OR SCI[Title/Abstract] OR spinal damage [Title/Abstract] OR spine damage [Title/Abstract] OR spine injury [Title/Abstract] OR spinal injury [Title/Abstract]). Syntax was adjusted accordingly for each database.

2.3 Screening/Extraction

Article screening was performed using an iterative approach, with 3 screeners (JMH, RZK, and SPE) participating in article selection and review. During the initial screen, the reviewers did not discuss the identity of the articles being considered for inclusion until the end of each screen. At least 2 of the screeners had to select each study for it to be included in the subsequent screen. There were 3 total

screens: 1) title and abstract, 2) full-text, and 3) full-text with data extraction. For the title and abstract screen, authors only had access to the titles and abstracts to determine relevant studies. During the title and abstract screen, all authors were instructed to examine the text for population, neurophysiological tests of SRC excitability and/or CST transmission, and measures of VAC and/or spasticity. The neurophysiological tests of SRC excitability included measures of H-reflex modulation: reciprocal inhibition, presynaptic inhibition, low-frequency depression, Ib inhibition, ratio of the maximum H-reflex to maximum direct motor response (H/M ratio) and cutaneomuscular -conditioned soleus H-reflexes. Neurophysiologic tests of CST transmission included MEP amplitude and latency. The VAC studies included functional measures such as: DF and PF strength, foot clearance during walking, tapping task, active range of motion (the range of joint movement through which the subject is able to volitionally move the ankle), walking distance, and walking speed. Spasticity studies included biomechanical measures of stretch-induced spastic responses such as: clonus duration, number of oscillations during clonus, and PF reflex threshold angle. If the abstract met all the inclusion criteria, then it was included in the full-text screen. For the full-text screen, authors assessed whether each study met inclusion criteria by skimming through each article once. Finally, during data extraction, the authors determined the relevance of the articles in a more in-depth manner by carefully reading the selected text, while simultaneously extracting specific information from each article. The following information was extracted from each article: study design, study aims, population, participant injury severity, neurophysiological tests, VAC and/or spasticity assessments, and the relationship, if any, between the last 2 measures. A hand search was conducted on citations in relevant review articles to identify additional articles during the first 2 screens, and on the articles assessed during the data extraction screen. During the final screen, review articles were excluded.

All articles selected for the final inclusion were grouped based on whether SRC excitability or CST transmission was assessed. The articles were further grouped by whether contributing authors utilized measures of VAC or measures of spasticity. Some articles **directly** determined the relationship between

neurophysiological measures and VAC and/or spasticity via correlation or linear regression analyses. In other articles there was no formal testing of the relationship between neurophysiological measures and VAC and/or spasticity. These latter articles were defined as having an **indirect** relationship.

3. Results:

3.1 Overview of included articles

In total, 1538 records were identified in the database searches. After duplicates and dissertations were removed, 454 articles remained, which were subjected to a title and abstract screen. Fifty-five articles were read in full following the title and abstract screen and 18 additional articles were removed for not meeting all inclusion criteria. The remaining 37 articles were assessed for eligibility during the data extraction phase, 22 of which were eliminated for being reviews or not meeting criteria. In addition to the 15 remaining articles, 2 articles were identified for inclusion during the hand search, bringing the total included article count to 17. Of the 17 included articles, 7 had interventional study designs, 10/17 contained measures to assess the relationship between SRC excitability and some aspect of VAC and/or spasticity, and 7/17 articles contained measures of the relationship between CST transmission and VAC. The screening process is illustrated in **Figure 2.2**.

The final 17 articles included in this review were published between 1994 and 2017. Neurophysiological data from 277 participants with SCI were captured across all studies. Some participants may be represented more than once, as some lead authors had multiple manuscripts included: Barthélemy (2 articles) (Barthelemy et al., 2013; Barthelemy et al., 2010), Manella (3 articles)(Manella & Field-Fote, 2013; Manella et al., 2013, 2017), and Wirth (4 articles) (Wirth et al., 2008a, 2008b, 2008c, 2008d). The number of SCI subjects per study ranged from 7 to 40 (median = 15).

Demographics of subjects enrolled in included studies. The majority of subjects had chronic SCI with an initial onset $\geq$12 months prior to study enrollment. Two of the 17 studies included only subjects with acute or subacute SCI (Piazza et al., 2016; Wirth et al., 2008d). Three studies included subjects with

subacute or chronic SCI (Wirth et al., 2008a, 2008b, 2008c). Of studies that reported subject sex, all had an equal or larger proportion of men to women. While all studies included subjects with motor-incomplete SCI, 6 also included subjects with motor-complete SCI (Adams & Hicks, 2011; Downes et al., 1995; Faist et al., 1994; Manella et al., 2017; Murillo et al., 2011; Smith et al., 2015). Most studies included a control group of non-injured or "healthy" participants (12/17),(Barthelemy et al., 2013; Barthelemy et al., 2010; Downes et al., 1995; Faist et al., 1994; Labruyere et al., 2013; Manella & Field-Fote, 2013; Murillo et al., 2011; Piazza et al., 2016; Wirth et al., 2008a, 2008b, 2008d; Yamaguchi et al., 2016), while 2 studies also included subjects with hemiplegia (Faist et al., 1994; Wirth et al., 2008b). Participant demographics for each included article are illustrated in **Table 2.2**.

SRC excitability articles. There were 10 studies that examined changes in SRCs. Four of 10 also included measures of VAC (Downes et al., 1995; Manella et al., 2013; Piazza et al., 2016; Yamaguchi et al., 2016); all 4 included correlation and/or association analyses to quantify the relationship between SRCs and VAC. Nine of 10 studies with SRC measures also had measures of ankle spasticity (Adams & Hicks, 2011; Downes et al., 1995; Faist et al., 1994; Manella & Field-Fote, 2013; Manella et al., 2013, 2017; Murillo et al., 2011; Piazza et al., 2016; Smith et al., 2015); only 6 of these articles included correlation and/or association analyses to quantify the relationship between SRC excitability and spasticity (Downes et al., 1995; Faist et al., 1994; Manella & Field-Fote, 2013; Manella et al., 2013, 2017; Piazza et al., 2016). There were 3/10 SRC articles that assessed both VAC and spasticity (Downes et al., 1995; Manella et al., 2013; Piazza et al., 2016).

CST transmission articles. There were 7 studies that examined changes in CST function, all of which included measures of VAC (Barthelemy et al., 2013; Barthelemy et al., 2010; Labruyere et al., 2013; Wirth et al., 2008a, 2008b, 2008c, 2008d). Six of 7 performed correlation and/or association analyses to quantify the relationship between CST function and VAC (Barthelemy et al., 2013; Barthelemy et al., 2010; Wirth et al., 2008a, 2008b, 2008c, 2008d). One study of CST transmission included subjects with stroke in addition to subjects with SCI without separating the data of those

individuals prior to performing linear regression analysis, making it difficult to parse out SCI results from results of participants with stroke (Wirth et al., 2008b). None of the studies examining CST transmission included measures of ankle spasticity.

3.2 Relationship between SRC excitability and VAC

Disrupted modulation of SRC excitability after SCI has been associated with decreased VAC. This impaired ability to voluntarily activate ankle DF can negatively impact walking function (Barthelemy et al., 2010). In the current review, 3/4 studies that included measures of SRC excitability and VAC (**Table 2.3**) provide evidence of a direct association between these measures (Manella et al., 2013; Piazza et al., 2016; Yamaguchi et al., 2016). All 3 studies that support a direct relationship between SRC excitability and VAC had interventional study designs (Manella et al., 2013; Piazza et al., 2016; Yamaguchi et al., 2016). Among the VAC measures included in these studies were foot clearance, foot tapping, DF strength, PF strength, active range of motion, and walking distance over time. Although evidence of an association between SRC excitability and VAC is clear, there was a wide range of SRC measures and interventions used across these studies (**Table 2.3**).

In contrast to the 3 interventional studies that provided evidence of a relationship between SRC excitability and VAC, the observational study captured during this review (Downes et al., 1995) assessed Ib inhibition from the medial gastrocnemius onto the soleus H-reflex. The authors concluded that Ib inhibition is not affected by SCI. This may suggest that the descending spinal circuits that modulate Ib SRCs differ from those that modulate IA SRC excitability.

3.3 Relationship between SRC excitability and ankle spasticity

The development of spasticity in the ankle PF is associated with poorer functional outcomes, interfering with ability to walk and perform daily tasks such as transfers (Adams & Hicks, 2005). Of the 9 studies with measures of ankle spasticity (**Table 2.4**), 6 provided evidence of an association with SRC excitability (Manella & Field-Fote, 2013; Manella et al., 2013, 2017; Murillo et al., 2011; Piazza et al., 2016; Smith et al., 2015). Only 4 of those 6 studies used statistical tests to quantify the relationship

between SRC excitability and spasticity (Manella & Field-Fote, 2013; Manella et al., 2013, 2017; Piazza et al., 2016). Five of the 6 studies that provided evidence of an association had an interventional design (Manella & Field-Fote, 2013; Manella et al., 2013; Murillo et al., 2011; Piazza et al., 2016; Smith et al., 2015). Overall, these 6 studies had a large spectrum of interventions, assessments of spasticity, and measures of SRC excitability (**Table 2.4**).

Additionally, the 2 studies that did not support an association between measures of spasticity and measures of SRC excitability were observational (**Table 2.4**) (Downes et al., 1995; Faist et al., 1994). One of these studies was described above in the section on VAC (Downes et al., 1995), wherein Ib inhibition from the medial gastrocnemius onto the soleus H-reflex was not found to be influenced by SCI. The authors likewise concluded that there was no relationship between excitability of this circuit and the Achilles tendon jerk reflex testing. The other study (Faist et al., 1994) assessed the level of heteronomous IA facilitation between the quadriceps and the soleus H-reflex amplitude as an index of presynaptic inhibition. The authors concluded that while there was less presynaptic inhibition in those with SCI, there was no relationship between the amount of presynaptic inhibition and the Ashworth scale scores. This conclusion directly conflicts with studies that have assessed presynaptic inhibition in other circuits and concluded that decreased presynaptic inhibition is associated with spasticity (Ashby et al., 1974; Calancie et al., 1993).

Of the 6 interventional studies with assessments of SRC excitability and ankle spasticity, only 1 did not provide evidence of an association (Adams & Hicks, 2011). In this study, clonus duration decreased more after body weight supported treadmill training compared to standing on a tilt table; however, there was no change in H/M ratio associated with either intervention. The lack of change in H/M ratio may be due to methodological issues, as prior studies have shown that the maximum H-reflex is less sensitive to modulatory influence than are submaximal reflex responses.

3.4 Relationship between CST transmission and VAC

Damage to the CSTs associated with SCI has been associated with deficits in walking ability and balance (Barthelemy et al., 2015). There is evidence that CST transmission is also related to VAC in all 7 of the articles in which the relationship between CST transmission and VAC was assessed (**Table 2.5**).

In contrast to the SRC studies, none of the CST transmission studies used an intervention; all had observational designs. Six of 7 studies used direct measures of correlations or linear regressions to assess the relationship between CST transmission and volitional measures (Barthelemy et al., 2013; Barthelemy et al., 2010; Wirth et al., 2008a, 2008b, 2008c, 2008d). Seven of 7 studies assessed MEP amplitude and latency in the TA. Functional measures including foot clearance, maximal movement velocity of the ankle, walking speed, walking distance over time, timing of dorsiflexion during walking, and ankle strength were all related to CST transmission. In 1 of these studies, a prospective cohort design was used to record longitudinal changes in the first 6 months after SCI. MEP amplitude, gait speed, DF muscle strength, and rate of activation increased significantly over time (Wirth et al., 2008d).

4. Discussion:

4.1 Summary - State of the Literature

While empirical evidence suggests there is an association between (1) measures of SRC excitability and VAC, (2) SRC excitability and spasticity, and (3) between CST transmission and VAC, the relationship between these measures in the literature is confounded by inherent variability in the neurophysiological measures and the wide range of functional measures utilized across the studies. To gain a better understanding of the evidence that does exist regarding the relationship between the underlying neurophysiological tests and ankle control, biomechanical and functional outcomes were more closely examined and compared to specific neurological tests within and between studies (**Table 2.3-5**).

4.2 Relationship between SRC excitability and VAC

After SCI, control of dorsiflexion depends on the extent to which hyperexcitability of the soleus SRCs degrades normal ankle kinematics. Ankle control can be examined using a variety of functional measures. It is important to determine the underlying mechanisms involved with each of these measures, as this knowledge could support the development of more effective rehabilitation strategies. The findings of this scoping review provide evidence that different components of ankle control may be associated with distinct measures of SRC excitability.

For the measure of ankle control during tapping tasks, 2 studies (Manella et al., 2013; Yamaguchi et al., 2016) support the conclusion that the number of repetitions of ankle movements during a timed tapping task is associated with H-reflex excitability as measured by presynaptic and reciprocal inhibition. The relationship between ankle strength and reflex excitability is less clear, as 2 studies indicate there could be an association between strength and amplitude of the conditioned H-reflex responses (Manella et al., 2013; Piazza et al., 2016), while another did not (Downes et al., 1995). In addition to the divergence of findings, and perhaps the reason for the divergence, the type of H-reflex test used for each of these studies varied (see **Table 2.3**). For the 2 studies that measured active range of motion in the ankles, the first study demonstrated a possible association between this functional outcome with low frequency depression and presynaptic inhibition (Manella et al., 2013), while the other demonstrated a change in SRC excitability, but not active range of motion (Yamaguchi et al., 2016). Lastly, in the study in which toe clearance during walking was measured, there was an association between change in toe clearance and reciprocal inhibition (Manella et al., 2013). Although most of these studies included correlations between SRC excitability and VAC measures, due to the variability of the tests, there is a strong need for additional studies to quantify the relationship between these two constructs.

4.3 Relationship between SRC excitability and ankle spasticity

The ability to achieve adequate dorsiflexion during functional tasks, such as walking and transfers, can be hindered by involuntary muscle contractions and stiffness associated with spasticity in the ankle plantar flexors. It is important to understand how commonly used tests of SRC excitability are

associated with common biomechanical measures of spasticity to develop more effective neuromodulatory strategies. In comparison to the number of studies that included measures of SRC excitability and VAC, there is a noticeably larger number of studies dedicated to measuring SRC excitability and ankle spasticity. There are several biomechanical assessments to measure ankle spasticity, including: spinal cord assessment tool for spastic reflexes (SCATS), Modified Ashworth Scale, Achilles tendon jerk reflex, and the ankle clonus drop test. These biomechanical tests can provide insight into properties such as ankle stiffness, clonus duration, and number of clonus oscillations. The large variety of biomechanical spasticity measures used across studies and the different types of SRC excitability measures utilized, make it difficult to quantify the relationship between the biomechanical measures of responsiveness to stretch and electrophysiologic SRC excitability measures. However, there is evidence that some biomechanical measures of spasticity may be associated with different components of SRC excitability (see **Table 2.4**).

One sensitive biomechanical measure of spasticity is the reflex threshold angle in the plantar flexors. One study provided evidence that reflex threshold angle appears to be related to reciprocal and presynaptic inhibition (Manella et al., 2013), while another showed it may be related to H-reflex excitability(Manella & Field-Fote, 2013). Of the 6 studies that included measures of clonus duration, 3 provide evidence that there may be a relationship between clonus duration and cutaneomuscular conditioned-reflex (Piazza et al., 2016), H-reflex excitability (Murillo et al., 2011), and low frequency depression (Manella et al., 2013). The same number of articles demonstrated the potential for an association between number of oscillations during ankle clonus and H-reflex excitability (Manella et al., 2017; Murillo et al., 2011; Smith et al., 2015). Only 1 study demonstrated some evidence of a relationship between ankle stiffness, measured using the Modified Ashworth Scale, and cutaneomuscular conditioned-reflex (Piazza et al., 2016). Although there is some evidence of an association between measures of SRC excitability and functional outcomes related to spasticity, an increased amount of attention into the

specifics of these measures and the underlying mechanisms that impact them is needed for a better understanding of this relationship.

4.4 Relationship between CST transmission and VAC

Spinal cord injury diminishes the capacity of the CST to transmit descending neural signals, thereby limiting both strength and speed of VAC in the dorsiflexors. Measures of VAC included: tapping tasks, ankle strength, toe clearance during walking, and gait measures. Both MEP amplitude and latency were shown to have some evidence of a relationship with each component of ankle control (see **Table 2.5**). It should be noted that although there were some differences in the methodologies used across studies, there was less variability between measures in the CST transmission studies than there were in the SRC excitability studies.

The coordination and timing of VAC can be assessed during tapping tasks to match a rhythmic tone. In the 4 studies that assessed VAC during tapping tasks, there was an association between maximal movement velocity and measures of CST transmission (Wirth et al., 2008a, 2008b, 2008c, 2008d). Ankle strength is another important component of VAC. For the measure of ankle strength, 2 articles demonstrated an association between strength with MEP latency (Wirth et al., 2008c) and MEP amplitude(Wirth et al., 2008d), while 2 other articles did not support a relationship between those measures (Labruyere et al., 2013; Wirth et al., 2008a). Foot drop/toe drag can be assessed by measuring toe clearance and ankle angle during swing phase. Toe clearance during walking was measured in 2 articles that assessed CST transmission (Barthelemy et al., 2013; Barthelemy et al., 2010). Both articles demonstrated that maximum toe elevation was associated with MEP amplitude and latency. Lastly, 4/6 studies, which contained some measure of gait parameters and stepping ability, presented evidence of an association with CST neurophysiology (Barthelemy et al., 2013; Barthelemy et al., 2010; Labruyere et al., 2013; Wirth et al., 2008a). Additional work is warranted in this area to understand how these measures of CST transmission relate to ankle spasticity, as none of these studies included any spasticity measures.

There would be great value in future studies that include CST transmission and SRC excitability measures in conjunction with ankle-related functional and biomechanical outcomes.

4.5 Existing Gaps- Limitations

4.5.1 Limitations of included studies

The greatest limitation in the currently available literature related to the relationships among CST transmission, SRC excitability, spasticity, and function was the large variability in measures used in the studies. Overall, there was a wider range of neurophysiological measures in the studies that assessed SRC excitability than the studies that assessed CST transmission. Although all of the reported neurophysiological measures assessed changes in SRC excitability, the studies tested different circuits at different timepoints, which may result in significant changes being observed in one study while non-significant results were observed in another. For example, although presynaptic inhibition and reciprocal inhibition both impact reflex excitability, the interneurons involved are not the same. Given that changes in the CST transmission can influence the SRC excitability, it is unfortunate that no articles included both corticospinal and spinal neurophysiological measures.

There was also variability in the types of measures used to assess spasticity and VAC in the studies which assessed SRC excitability and the articles that assessed CST transmission. In the articles that addressed SRC excitability, the studies included different biomechanical measures of ankle spasticity. None of the included CST transmission articles assessed spasticity. Both measures are important for assessing factors that influence changes in gait parameters after injury. Increases in voluntary control and decreases in spasticity are both beneficial for improving walking function in persons with SCI. Future studies should assess both volitional and spasticity related measures of the ankle.

4.5.2 Limitations of review

The search strategy was potentially limited for 2 main reasons. The search included only studies of SRC excitability that used measures based on the H-reflex test and studies of CST transmission that

used MEPs as neurophysiological measures. Studies which utilize other neurophysiological measures along with VAC and spasticity measures may have been excluded, potentially limiting the scope of this review. We chose to use H-reflex and MEPs as the primary measures of interest because they are both widely used, non-invasive neurophysiological tests with good reliability. However, despite being commonly used measures, H-reflexes and MEPs cannot isolate or provide information about the integrity of all pathways that may influence neuromotor control of the ankle (i.e. rubrospinal tract, reticulospinal tract, vestibulospinal tract, and group II afferent nerve pathways).

5. Conclusions

Based on the available literature there is evidence of an association between neurophysiological excitability with VAC and spasticity after SCI. Future studies assessing these relationships are important for the development of better targeted therapies such as whole body vibration, peripheral nerve somatosensory stimulation, and transcranial direct current stimulation to improve walking and balance in individuals affected by SCI. There is great potential for this knowledge to guide therapists in the use of non-invasive stimulation to increase descending drive or decrease spasticity. While it may be difficult to isolate interventions to either CST transmission or SRC excitability alone, it is important to understand neurophysiologic contributions to ankle control given its relevance to safe and efficient ambulation within clinical populations with central nervous system disorders. Studies which employ a battery of neurophysiologic and functional measures to assess both SRC excitability and CST transmission in persons with SCI are warranted.

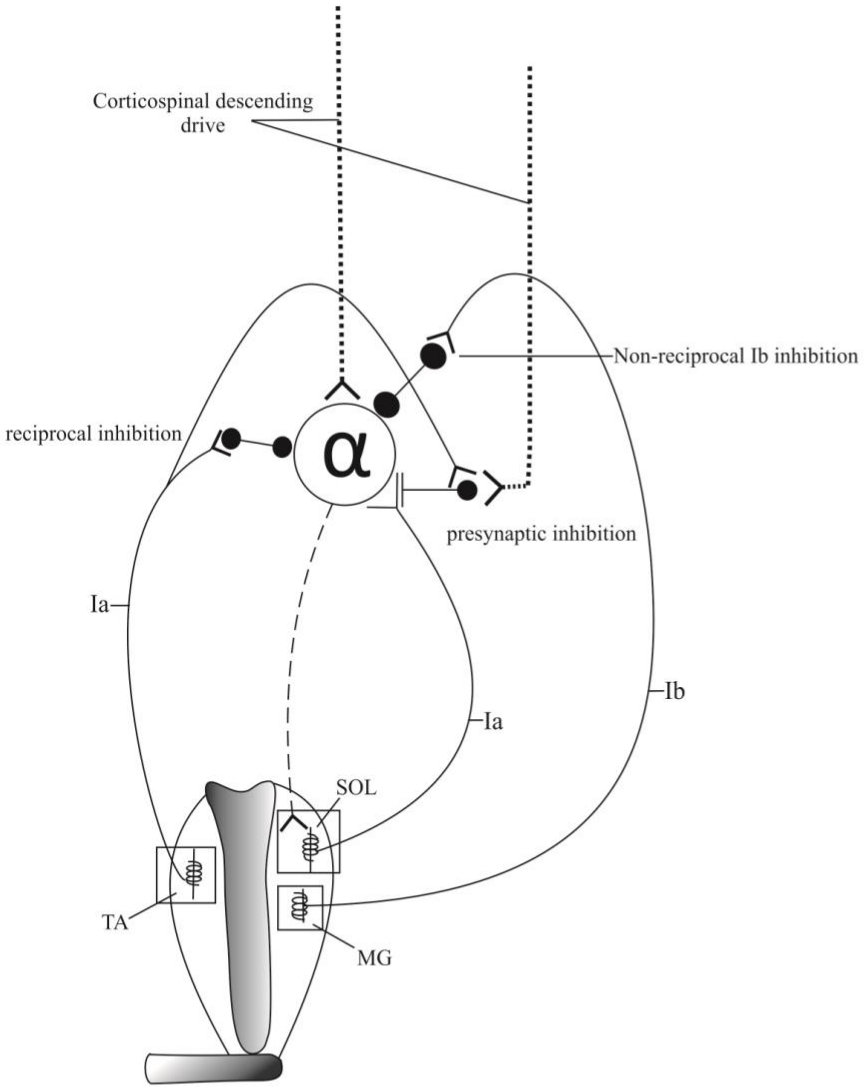

Figure 2.1 Spinal pathways that likely contribute to ankle control and the development of spasticity including reciprocal inhibition, presynaptic inhibition, and non-reciprocal Ib inhibition.

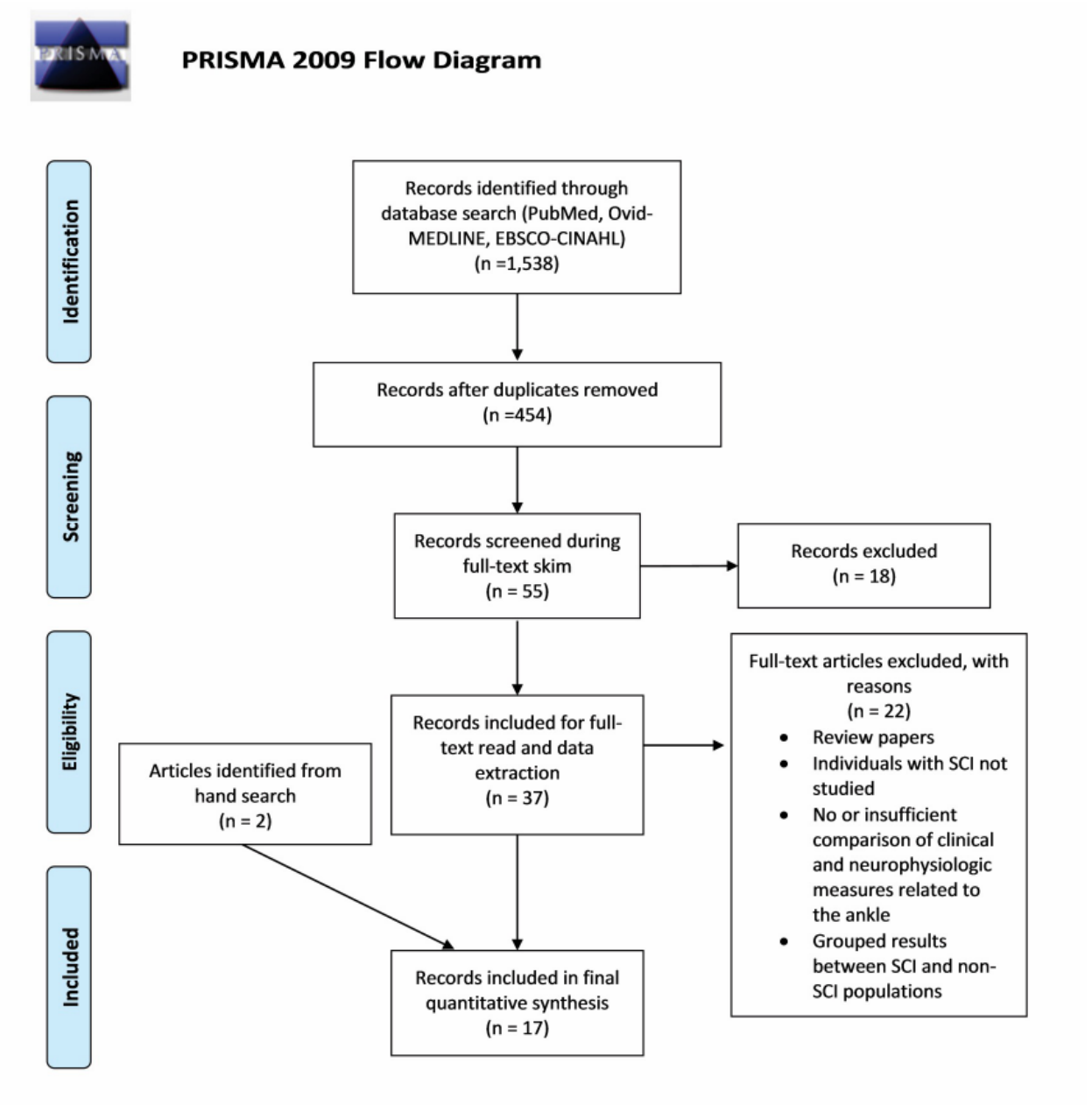

Figure 2.2 PRISMA Flow Diagram. PRISMA Flow Diagram of the Screening process followed during the scoping review. From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097
For more information, visit www.prisma-statement.org.

Table 2.1 Detailed search terms. The initial search term categories were combined in the following ways across 3 databases: 1. SCI + CST+ Spinal+ DF+PF, 2. SCI + CST + DF, 3. SCI + CST + PF, 4. SCI + Spinal + DF, and 5. SCI + Spinal + PF

Search category	Search terms
SCI	(Spinal Cord Injury [Title/Abstract] OR SCI[Title/Abstract] OR spinal damage [Title/Abstract] OR spine damage [Title/Abstract] OR spine injury [Title/Abstract] OR spinal injury [Title/Abstract])
CST	(Corticospinal Excitability OR CST OR Corticospinal OR corticospinal descending drive OR corticospinal OR TMS OR transcranial magnetic stimulation)
SPINAL	(spinal reflex circuit OR reflex OR Hoffmann reflex OR H-reflex OR hyperreflexia OR hypertonia OR spinal reflex OR stretch reflex OR monosynaptic reflex)
DF	Control of ankle dorsiflexor OR ankle OR dorsiflexor OR tibialis anterior OR TA OR walking/physiology [MeSH Terms] OR Ankle joint/physiopathology [MeSH Terms] OR Ankle joint/innervation [MeSH Terms] OR Exercise therapy/methods [MeSH Terms] OR Gait Disorders [MeSH Terms] OR Gait [MeSH Terms])
PF	((Control of ankle plantar flexors OR ankle OR plantar flexors OR soleus OR walking/physiology [MeSH Terms] OR Ankle joint/physiopathology [MeSH Terms] OR Ankle joint/innervation [MeSH Terms] OR Exercise therapy/methods [MeSH Terms] OR Gait Disorders [MeSH Terms] OR Gait [MeSH Terms]))

SCI: spinal cord injury; CST: corticospinal tract; DF: dorsiflexors; PF: plantar-flexors

Table 2.2 Study characteristics and participant demographics

SRC or CST	Authors	Study Aims	ISNCSCI grades	Clinical description	Mean TPI	SCI sample size(sex distribution)	Mean age of SCI subjects (y)	Non-SCI participant sample size (sex distribution)	Mean age of Non-SCI participants (y)
SRC	Manella et al. 2017	Examine reliability and construct validity of drop test to quantify ankle clonus in persons with SCI and compare results with the SCATS and H/M ratio	A to D	C2 to L1 LOI, Evidence of clonus	8.9y	n= 40 (31 M, 9 F)	39.6±13	N/A	N/A
	Piazza et al. 2016	Examine the effects of leg-cycling on conditioned H-reflex excitability and how it relates to lower extremity function after miSCI	C to D	C5-T10 LOI, capable of cycling	16±3 weeks	n= 9 (6 M, 3 F)	44±5	Non-injured: n=10	34±3
	Yamaguchi et al. 2016	Compare effect of anodal tDCS and PES on RI and ankle movement in miSCI	C to D	C1 to T11, 1+ PF spasticity (MAS)	4.5± 4.2 y	n=11 (11 M)	51.8± 10.7	Non-injured: n=10	50.7±8.9
	Smith et al. 2015	Assess changes in H-reflex in different positions after locomotor training in persons with SCI	A to D	C1 to T10 LOI	4.3y	n=15 (10 M, 5 F)	37.53	N/A	N/A
	Manella and Field-Fote 2013	1. Investigate effects of LT on measures of spasticity and walking. 2. Assess association of change in walking speed with measures of reflex activity 3. Establish sensitivity to change and validity of PF RTA	C or D	C4 to L1 LOI, Evidence of clonus in some participants	8.9y	Locomotor cohort: n=18 (16 M, 2 F) Validity cohort: n=40 (30 M, 10 F)	Locomotor cohort: 35.1 Validity cohort: 39.3	Non-injured: n=10	27.3
	Manella et al. 2013	1. Examine effects of different operant conditioning interventions on ankle motor control, spasticity, and walking related measures in persons with miSCI. 2. Explore relationship between changes in neurophysiological and clinical outcome measures.	D	Positive ankle clonus, Median LL of TA group: C7; Median LL of SOL group: C5	TA group: 10.8±10.0y; SOL group: 10.8±08.8y	Total: n=12; TA cohort: n=6 (6M); SOL cohort: n=6 (4 M, 2 F)	TA cohort: 44.2; SOL cohort: 45.2	N/A	N/A
	Adams and Hicks 2011	Examine effects of BWSTT and TTS on spasticity and motor neuron excitability in chronic SCI	A to C	C5 to T10 LOI, stable spasticity, primary wheelchair user	5.0±4.4y	n=7 (6 M, 1 F)	37.1±7.7	N/A	N/A
	Murillo et al. 2011	Examine the effect of RF vibration on clinical and neurophysiological outcome measures of spasticity in SCI	A to D	C3 to T11 LOI; lower limb spasticity ≥ 1.5 (MAS)	5.6y±1.9 months	n=19 (16 M, 3 F)	36.0±10.6	Non-injured: n=9	33.8±9.4
	Downes et al. 1995	Examine reflex actions of MG group Ib afferent stimulation on SOL H-reflex excitability and spasticity in persons with SCI	Both cSCI and iSCI	C4 to T10 LOI	16mos	n=13 (11 M, 2 F)	30	Non-injured: n=20	25
	Faist et al. 1994	Assess effect of femoral nerve stimulation on SOL H-reflex activity in SCI. Examine association of spasticity and PI	Both cSCI and iSCI	LOI not reported	27.5mos	n=17	34.8	Non-injured: n=28, Hemiplegic: n=18	Non-injured age range: 21-59; Hemiplegic mean age: 49.6

Table 2.2 Study characteristics and participant demographics (continued)

SRC or CST	Authors	Study Aims	ISNCSCI grades	Clinical description	Mean TPI	SCI sample size(sex	Mean age of SCI subjects (y)	Non-SCI participant sample size (sex	Mean age of Non-SCI participants
CST	Barthélemy et al. 2013	Examine the correlation of CST function and measures of gait and ankle function after SCI	D	C1 to L1 LOI	12y	n=24 (22 M, 2 F)	43.4	Non-injured: n=11	45
	Labruyère et al. 2013	Assess deficits in quick and accurate movements in miSCI by combining TMS, EMG, and a response time task and comparing differences in clinical characteristics.	D	T2 to L4 LOI only	T2 to L4 LOI only	n=15 (10 M, 5 F)	50.2±12.4	Non-injured: n=15	50.1±12.3
	Barthélemy et al. 2010	Examine the relationship between parameters that may reflect CST function and physical foot drop deficit observed after SCI	D+	C to L LOI; ability to walk 10m	C to L LOI; ability to walk 10m	n=24 (22 M, 2 F)	43±14	Non-injured: n=15	42±16
	Wirth et al. 2008a	Examine ankle DF timing during gait and in supine to CST conductivity and measures of strength and gait speed in persons with and without SCI.	C or D	C2 to T12	C2 to T12	n=12 (9 M, 3 F)	58.3±10.7	Non-injured: n=12	59.2±11.3
	Wirth et al. 2008b	Examine the effects of CST damage on ankle dexterity and MMV in individuals with miSCI and stroke	miSCI	C3 to L5 LOI	C3 to L5 LOI	n=12 (6 M, 6 F)	62.3±8.3	Stroke: n=12; Non-injured: n=12	Stroke 65.8±10.5; Non-injured: 63.3±10.7
	Wirth et al. 2008c	Examine the relationship between ankle dorsiflexor strength, MVC, and MMV with CST integrity and with walking capacity in persons with miSCI	C or D	C3 to L1 LOI	C3 to L1 LOI	n=26; strength +MEP n=17 (14 M, 3 F); strength + gait n=19 (14 M, 5 F)	Strength + MEP cohort: 50.8±16.5; strength + gait speed cohort: 54.3±15.2	N/A	N/A
	Wirth et al. 2008d	Examine recovery of ankle DF in miSCI via neurophysiological assessment of CST function and functional parameters	C or D	C3 to T12 LOI	C3 to T12 LOI	n=12 (6 M, 6 F)	53.7±18.5 months	Non-injured: n=12	54.0±18.0

Table 2.2: [+] One subject lacked sacral sparing and had an AIS A classification, but had motor function equivalent to AIS D
Abbreviations: SRC, Spinal Reflex Circuitry; CST, corticospinal tract; ISNCSCI, International Standards for Neurological Classification of Spinal Cord Injury; TPI, time post-injury; SCI, spinal cord injury; SCATS, Spinal Cord Assessment Tool for Spastic Reflexes; LOI, level of injury; N/A, not applicable; miSCI, motor incomplete spinal cord injury; tDCS, transcranial direct current electrical stimulation; PES, patterned electrical stimulation; RI, reciprocal inhibition; MAS, Modified Ashworth Scale; LT, locomotor training; PF, plantar flexor; RTA, reflex threshold angle; LL, lesion-level; TA, tibialis anterior; SOL, soleus; BWSTT, body-weight supported treadmill training; TTS, tilt table standing; RF, rectus femoris; cSCI, complete spinal cord injury; iSCI, incomplete spinal cord injury; MG, medial gastrocnemius; PI, presynaptic inhibition; TMS, transcranial magnetic stimulation; EMG, electromyography; MMV, maximal movement velocity; MVC, maximal voluntary contraction; MEP, motor evoked potential; DF, dorsiflexion

Table 2.3 Is there a relationship between SRC excitability and volitional ankle control?

Authors	Study Design	Intervention	Electrophysiological Measure	Relevant Functional Measure	Direct or indirect evaluation of association?	Evidence of Association ?
Piazza et al. 2016	Interventional	Leg-cycling	Plantar cutaneomuscular conditioned SOL H-reflex	Strength (TA and Triceps Surae manual muscle score)	**Direct** (Multiple Stepwise Forward Regression and Spearman's Correlation)	Yes
Yamaguchi et al. 2016	Interventional	Anodal tDCS combined with PES	SOL H-reflexes in response RI and PI	Ankle movement/tapping, Active ankle ROM	**Direct** (Pearson's correlation)	Yes
Manella et al. 2013	Interventional	Operant conditioning: TA EMG activation increase OR SOL H-reflex decrease	SOL H-reflexes in response to RI, PI, and LFD	Toe/foot clearance during walking, ankle movement/tapping, strength (DF and PF), active ROM (DF)	**Direct** (Spearman's correlation**)**	Yes
Downes et al. 1995	Observational	N/A	Ib conditioned-SOL H-reflex	Strength (DF and PF)	**Direct (**Pearson's correlation)	No

Abbreviations: SOL, soleus; TA, tibialis anterior; tDCS, transcranial direct current stimulation; PES, patterned electrical stimulation ; RI, reciprocal inhibition; PI, presynaptic inhibition; ROM, active range of motion; EMG, electromyography; LFD, low frequency depression; DF, dorsiflexor; PF, plantar flexor

"Yes" indicates that there is some evidence that at least one electrophysiological measure had an association with at least one relevant functional measure

Table 2.4 Is there a relationship between SRC excitability and ankle spasticity?

Authors	Study Design	Intervention	Electrophysiological Measure	Relevant Functional Measure	Direct or indirect evaluation of association?	Evidence of Association?
Faist et al. 1994	Observational	N/A	PI (Quadriceps), SOL H/M ratio	Hypertonia (Achilles tendon jerk reflex, Ashworth scale)	**Direct (Pearson's correlation)**	No
Downes et al. 1995	Observational	N/A	Ib conditioned-SOL H-reflex	Hypertonia (Achilles tendon jerks; tone of the ankle DF, PF)	**Direct (Pearson's correlation)**	No
Adams and Hicks 2011	Interventional	BWSTT v. TTS	SOL H/M ratio	Clonus duration (SCATS-Clonus)	**Indirect**	No
Murillo et al. 2011	Interventional	Focal vibration (RF)	SOL H/M ratio	Clonus duration and # of oscillations	**Indirect**	Yes
Manella and Field-Fote 2013	Interventional AND Observational	Locomotor training	SOL H/M ratio	Clonus duration, # of oscillations, PF RTA (Drop test), gait speed	**Direct (Spearman's correlation)**	Yes
Manella et al. 2013	Interventional	Operant conditioning: TA activation increase OR Soleus H-	SOL H-reflex: RI, PI, and LFD	Clonus duration, PF RTA	**Direct (Spearman's correlation)**	Yes
Manella et al. 2017	Observational	N/A	SOL H/M ratio	# of oscillations (Drop test)	**Direct (Spearman's correlation)**	Yes
Smith et al. 2015	Interventional	Locomotor training (Lokomat)	SOL H/M ratio	Clonus duration and # of oscillations (via soleus EMG analysis during walking)	**Indirect**	Yes
Piazza et al. 2016	Interventional	Leg-cycling	Plantar cutaneomuscular conditioned SOL H-reflex	Hypertonia (MAS), clonus duration (SCATS clonus score)	**Direct (Multiple Stepwise Forward Regression and Spearman's Correlation)**	Yes

Abbreviations: PI, presynaptic inhibition; SOL, soleus; DF, dorsiflexor; PF, plantar flexor; BWSTT, body-weight supported treadmill training; TTS, tilt table standing; SCATS, Spinal Cord Assessment Tool for Spastic Reflexes; RF, rectus femoris; RTA, reflex threshold angle; EMG, electromyography; RI reciprocal inhibition; PI, presynaptic inhibition; LFD, low frequency depression

"Yes" indicates that there is some evidence that at least one electrophysiological measure had an association with at least one relevant functional measure

Table 2.5 Is there a relationship between CST transmission and volitional ankle control?

Authors	Study Design	Intervention	Electrophysiological Measure	Relevant Functional Measure	Direct or indirect evaluation of association?	Evidence of Association?
Barthélemy et al. 2013	Observational	N/A	TA MEP amplitude, latency	Gait kinematics toe clearance, gait speed, walking distance	Direct (Spearman's and Pearson's correlation)	Yes
Labruyère et al. 2013	Observational	N/A	MEP amplitude, latency	Muscle strength (DF and PF), stepping task	Indirect	Yes
Barthélemy et al. 2010	Observational	N/A	TA MEP amplitude, latency	Gait kinematics – foot drop	Direct (Spearman's and Pearson's correlation)	Yes
Wirth et al. 2008 A	Observational	N/A	MEP amplitude, latency	Timing of ankle dorsiflexion during gait and in supine at 3 frequencies, DF MMV, TA muscle strength (MVC)	Direct and Indirect (Spearman's correlation)	Yes
Wirth et al. 2008 B	Observational	N/A	TA MEP amplitude, latency	Ankle dexterity, MMV	Simultaneous Direct (linear regression analyses-backward standardized regression GROUPED TOGETHER)	Yes
Wirth et al. 2008 C	Observational	N/A	MEP amplitude, latency	TA muscle strength (AIS motor score, MVC), DF MMV, gait speed, walking ability (WISCI)	Direct (Linear, backwards multiple regression)	Yes
Wirth et al. 2008 D	Observational	N/A	MEP amplitude, latency	ankle dexterity, MMV, TA strength (AIS motor score, MVC), gait speed	Direct (Linear regression and Spearman's correlation)	Yes

Abbreviations: TA, tibialis anterior; MEP, motor evoked potential; DF, dorsiflexor; PF, plantar flexor; MMV, maximal movement velocity; MVC, maximal volitional contraction; AIS, ASIA impairment scale; WISCI, Walking Index for Spinal Cord Injury. "Yes" indicates that there is some evidence that at least one electrophysiological measure had an association with at least one relevant functional measure

Chapter 3: Impact of Whole Body Vibration on Dorsiflexion during Swing Phase and Plantar Flexor Reflex Modulation in Persons with SCI

1. Introduction:

One of the most obvious consequences after spinal cord injury (SCI) is the loss or impairment of walking ability. For this reason, it is not surprising that regaining the ability to walk is a top priority for persons with SCI (Ditunno et al., 2008). An important component of walking that is especially affected after SCI is the ability to lift the forefoot during swing phase (Barthelemy et al., 2015). This inability to achieve adequate dorsiflexion, known clinically as foot drop, can be further hindered by the involuntary muscle contractions and stiffness associated with spasticity in the plantar-flexors. To optimize functional independence and improve quality of life in persons with SCI, it is important to understand the neurophysiological mechanisms that contribute to these deficits in ankle control, and how they respond to interventions that modulate neural excitability.

The volitional control of the dorsiflexors is more highly dependent on corticospinal drive than are other lower extremity muscles (Capaday et al., 1999; Schubert et al., 1997). Foot drop is a result of disrupted descending drive from the corticospinal tract (CST) to the tibialis anterior (TA) due to damage to the spinal cord. Additionally, this damage can lead to spasticity in the plantar-flexors, which is associated with reduced ability to activate the TA and adds to the impairment of ankle control during walking (Manella et al., 2013). In persons with SCI, interventions that either increase descending drive to the TA or decrease spasticity in the soleus are associated with improved walking function (Manella et al., 2013).

In persons with SCI, whole body vibration (WBV) decreases spasticity (Estes et al., 2018; Ness & Field-Fote, 2009a), and improves spinal reflex modulation (Sayenko et al., 2010). Additionally, WBV has been associated with increased strength (Bosveld & Field-Fote, 2015) and improved walking ability (Ness & Field-Fote, 2009b). Effects of WBV on walking ability and spasticity have been shown to persist into the week following a course of WBV (Ness & Field-Fote, 2009a, 2009b). However, effects of WBV have

been shown to be dependent on dosage parameters, such as frequency and duration (i.e., number of bouts). The purpose of the current study in participants with motor-incomplete SCI was to investigate whether the influences of WBV on increasing CST excitability and decreasing reflex excitability would have a persistent impact on dorsiflexion during swing phase and/or decreased plantar-flexor reflex excitability.

2. Materials and Methods:

This study was carried out with the ethics approval from the Shepherd Center Research Review Committee. All participants provided written informed consent prior to study enrollment in accordance with the Declaration of Helsinki and the study was conducted in accordance with the Health Insurance Portability and Accountability Act guidelines. The current study is a supplemental analysis of data collected as part of a larger study focused on dose-response effects of WBV on spasticity in persons with SCI. This study was registered with clinicaltrials.gov (NCT02340910).

2.1 Participants

Individuals were eligible for participation in the study if they met the following inclusion criteria: 16-72 years of age, $\geq$ 6 months since time of spinal cord injury, have at least mild spasticity affecting lower extremity muscles (as determined by participant self-report), able to sit at the edge of the mat without assistance of another person, able to tolerate standing for at least 1 minute, able to walk 10 meters without the use of ankle foot orthosis, and presence of a measurable H-reflex during electrophysiological testing. Individuals were excluded for the following reasons: progressive or potentially progressive spinal lesions, neurological level of injury below spinal level T12, history of cardiovascular irregularities, problems following instructions, and orthopedic conditions that would limit their participation in the protocol (e.g., knee or hip flexion contractures > 10°).

2.2 Study Design

To assess the dose-response effects of WBV, a randomized, sham-control wash-in study design was used with baseline testing (T1) followed by a 2-week sham-stimulation wash-in phase, pre-WBV testing (T2) followed by a 2-week WBV intervention phase, and finally, post-WBV testing (T3) (**Table 1**). During the sham-stimulation wash-in phase all participants received 10 sessions of sham-stimulation (every weekday for 2 weeks). During the WBV intervention phase they received 9 sessions of WBV treatment over 2 weeks (with T3 before the 10th session). Participants were randomized to either short- or long-bout groups, based on the number of bouts during the WBV intervention phase, each bout consisted of a 45-second period of standing on the WBV platform followed by a 1-minute rest. This stand/rest period has been used in a prior study of WBV wherein beneficial effects were reported (Estes et al., 2018). The number of bouts during the WBV intervention phase was counterbalanced with the number of bouts during the sham-stimulation wash-in phase. In this way, the short-bout group received 16 bouts/session of sham-stimulation followed by 8 bouts/session of WBV and the long-bout group received 8 bouts/session of sham-stimulation followed by 16 bouts/session of WBV. Electrophysiological, spasticity, and functional data were collected during each testing session. For this study, data related to the sham-stimulation wash-in phase (T1 to T2) was compared to data in the WBV intervention phase (T2 to T3).

2.3 Intervention

2.3.1 Sham-Stimulation Wash-In Phase (T1-T2)

The sham-stimulation wash-in phase was intended to control for the possible effect of standing and/or repeated performance of the sit-to stand maneuver on reflex modulation and dorsiflexion during walking. The wash-in phase is especially important because there is evidence that activity (Field-Fote et al., 2021), and specifically the sit-to-stand maneuver, impacts spasticity (Estes et al., 2018). During each sham-stimulation bout, participants stood on the WBV platform (Powerplate Pro 5, Performance Health Systems, LLC, Northbrook, IL) for 45 seconds with a slight squat posture and were encouraged to use the handrails for balance only. Each bout was followed by 1 minute of rest in a seated position.

The sham-stimulation intervention was provided by 2-inch round electrodes adhered to the posterior thoracic region (on the inferior angle of the scapula). The stimulator (Empi Continuum, DJO Global, Vista, CA, USA) was turned on and intensity increased until the participant indicated that they could feel the stimulation. Participants were then instructed that the stimulation would be reduced to an intensity that they could not feel, but in fact, the stimulator was turned off. While prior studies have suggested that there is no influence of stimulation when intensity is below sensory threshold (Conforto et al., 2007; Conforto et al., 2002), the rationale for turning the stimulation off completely was that in the presence of SCI, the lesion could prevent the participant from feeling the stimulation, such that intensities below sensory threshold could still be high enough to influence the excitability of spinal circuits.

2.3.2 Whole Body Vibration Phase (T2-T3)

For the WBV phase of this study, participants received high frequency (50Hz) WBV. This frequency was chosen based on the results of a prior study indicating that 50Hz has a larger antispasmodic effect compared to 30Hz in persons with SCI (Estes et al., 2018). The WBV bout consisted of standing on the WBV platform in the same posture and for the same duration/intervals as described for the sham condition. After each bout of vibration, participants rested in a seated position for 1 minute.

2.4 Outcome Measures

All tests were performed on the more spastic leg as determined by participant response to the query “which of your legs is more spastic?”.

2.4.1 Dorsiflexion During Swing Phase

Control of ankle dorsiflexion during walking was assessed based on kinematic data captured using inertial measurement units (IMUs; Xsens Technologies, Enschede, Netherlands), with sensor placements consistently attached to the pelvis at the center of the back at the height of the anterior superior iliac spine, and bilaterally to the middle of the lateral thighs, tibias, and inside the shoe laces across all tasks in accordance with the manufacturer guidelines (MVN User Manual 2020, Xsens

Technologies). Participants performed 3 trials of walking along a 10-meter walkway, following the instruction “walk as quickly and safely as you can”. Kinematic measurements captured by the IMU software were then exported for analysis. Sagittal ankle angle at mid-swing was determined for each step cycle of the more spastic leg.

2.4.2 Reflex Modulation

Modulation of spinal reflex excitability was assessed based on low-frequency depression of the soleus H-reflex. Participants were positioned reclined on padded mat with legs extended and 2 wedges providing back support. To record electromyographic data, the participants’ skin was cleaned with alcohol and abrasive paste, then bipolar electrodes (AgCl; Motion Lab Systems, Baton Rouge, LA) were placed over the soleus in the area corresponding to the central portion of the muscle of the most spastic leg (Botter & Vieira, 2017). Signals were captured at a 2000Hz sampling rate (Spike CED, Cambridge Electronics Design). An H-reflex recruitment curve was constructed for each participant based on standard procedures (Manella et al., 2013). Briefly, square-wave pulses with intensity below reflex threshold were directed at the posterior tibial nerve with a 5-second interstimulus interval between each pulse until a maximum M-wave was recorded. Stimulus amplitude was increased in increments of 2.5 mA pre-H-wave threshold (50 μV), increased to 5mA post-threshold, and finally by 10 mA after H-max was identified. Based on the recruitment curve, the stimulation intensity at which the H- wave was 10-30% of the maximum M-wave was used to assess low-frequency depression (Crone et al., 1990). For low-frequency depression data acquisition, each trial consisted of a test pulse to the posterior tibial nerve followed by a train of 10 conditioned stimuli at a 1-second interstimulus interval. At least 4 trials were averaged for each participant based on the criteria of having an H-wave at 10-30% of the maximum M-wave during the test pulse.

2.5 Data Analysis

For continuous measures, the mean and standard deviation were calculated using Excel and displayed as mean (standard deviation). For categorical measures, the median and range were displayed as median (range). Data were analyzed using SPSS (version 26-28; SPSS Inc., Chicago, IL, USA). A paired sample t-test was used to analyze within- and between- phase differences in functional and electrophysiological measures for the sham-stimulation wash-in phase (T2 – T1) and the WBV intervention phase (T3 – T2). Pearson's correlations were used to assess all relevant associations.

To calculate dorsiflexion during swing phase, the middle 50 percent of steps were analyzed to remove any impact of acceleration and deceleration during each walk. Sagittal ankle angles at mid-swing were extracted from the sensor data, where positive angles indicated dorsiflexion and negative ankle angles indicated plantarflexion. For soleus H-reflex peak-to-peak amplitude, μV, was measured and low-frequency depression percentage was calculated as (Average of the 10 conditioned stimuli / test stimulus) *100%. Values lower than 100 are indicative of inhibition, while values greater that 100 are indicative of facilitation. Lower percentage of low-frequency depression is indicative of increased inhibition in the plantar-flexor spinal reflex, which is what we predicted to occur after WBV.

There were no differences between the short- and long-bout WBV groups in ankle angle at T1 (t_{14} = - 0.47, p = 0.32), within T2 – T1 (t_{14} = 0.69, p = 0.25), T3 – T2 (t_{14} = 0.1, p = 0.46) or T3 – T1 (t_{14} = 0.791, p = 0.221) . Likewise, there were no between-groups differences in low-frequency depression percentage at the testing timepoints T1 (t_{14} = 0.095, p = 0.463), T2 – T1 (t_{14} = - 0.19, p = 0.492), T3 – T2 (t_{14} = - 0.15, p = 0.441), or T3 – T1 (t_{14} = - 0.193, p = 0.425) therefore short- and long-bout data were pooled for all analyses.

Possible differences in responsiveness due to baseline dorsiflexion ability were also examined. Data from the participants who were able to achieve dorsiflexion (i.e., positive ankle angles) during swing phase at baseline (T1) were compared to data from participants whose ankles remained in plantarflexion (i.e., negative ankle angles) during swing phase.

3. Results:

3.1 Demographics

Sixteen participants (6 Female) from the larger study were able to walk 10 meters without use of an ankle foot orthosis and had a measurable H-reflex, thereby meeting the inclusion criteria for this analysis (**Table 3.2**). The mean age was 51.13 (14.57) years with an average time of 6.24 (8.23) years since injury. All participants were classified as having American Spinal Injury Association (ASIA) impairment scale (AIS) score of AIS D. Neurological level of injury varied from C2 to T8. The median total lower extremity motor score was 45 (range: 26 – 50) out of 50, with a median of 21 (range: 9 – 25) for the weaker side and 24 (range: 14 – 25) for the stronger side. Eight participants were randomized into the short-bout group while the other 8 participants were randomized into the long-bout group.

3.2 Dorsiflexion During Swing Phase

There were no significant between- or within-phase differences in dorsiflexion angle during swing phase (**Figure 3.1**). In all cases, all group differences were less than the range of error of the measurement (1 – 2.15 degrees; (Robert-Lachaine et al., 2017; Zhang et al., 2013). Between phases, there was a 0.52 (6.01) degrees average nonsignificant difference ((T3 – T2) – (T2 – T1) $t_{15} = 0.34$, $p = 0.37$). On average, there was a nonsignificant difference of – 0.32 (3.76) degrees within T2 – T1 ($t_{15} = -0.34$, $p = 0.37$) and 0.2 (3.28) degrees within T3 – T2 ($t_{15} = 0.24$, $p = 0.41$). For dorsiflexion angles during swing phase, there was a strong positive correlation between T1 vs. T2 ($r = 0.72$, $p < 0.001$) and T2 vs. T3 ($r = 0.79$, $p < 0.001$) suggesting that this measure is stable over time in most participants.

At T1, most participants (10/16) displayed plantarflexion in the period leading up to mid-swing (**Table 3.3**), however 6 participants were able to achieve some swing phase dorsiflexion at baseline. Following the WBV phase, both groups displayed small nonsignificant differences in the direction of greater dorsiflexion but with a smaller difference in the group that initially displayed plantarflexion (0.1 (2.7) degrees versus 0.4 (4.4) degrees for the group that showed some dorsiflexion at baseline.

3.3 Reflex Modulation

There were no significant between- or within- phase differences in soleus H-reflex low-frequency depression percentage (**Figure 3.2, Table 3.3**). Between phases there was a -2.19 % (50.62) nonsignificant difference ((T3 – T2) – (T2 – T1) t_{15} = -0.17, p = 0.43). Within T2 – T1, there was a 2.33 % (28.51) nonsignificant difference (t_{15} = 0.33, p = 0.374) and 0.14 % (27.61) nonsignificant difference within T3 – T2 (t_{15} = - 0.02, p = 0.492). For low-frequency depression percentage, there was a significant moderate positive correlation between T1 vs. T2 (r = 0.43, p = 0.05) and approached significance T2 vs. T3 (r = 0.42, p = 0.053), suggesting that this measure is also stable over time in most participants.

4. Discussion:

4.1 Dorsiflexion during Swing Phase

In this analysis, a persistent influence of short- or long-bout WBV on ankle dorsiflexion during walking was not identified. Based on previous studies in which WBV increased CST descending drive to lower extremity muscles (Krause et al., 2016; Mileva et al., 2009) and the fact that CST has the strongest connection with ankle dorsiflexors during walking (Capaday et al., 1999) it was expected that WBV would be associated with increased dorsiflexion during swing phase. Moreover, it was expected that the effects of WBV would be dose-dependent, such that participants in the long-bout group would have a greater increase in dorsiflexion during swing phase when compared to the short-bout group. Neither hypothesis was supported by the data; differences were small and within the range of measurement error.

A previous report of the effect of WBV on walking function in participants with SCI identified persistent changes through the week following the last intervention. In that study participants received 3 sessions per week of WBV for 4 weeks for a total of 12 sessions (Ness & Field-Fote, 2009b). The changes in walking speed observed in the prior study may have been unrelated to improvements in dorsiflexion during swing phase. Alternatively, while the cumulative dose of WBV in the current study was similar to that in the prior study, failure to identify effects of WBV in this study may be due the

distribution of the WBV dose, which was distributed over a longer time period in the prior study. Additionally, there may be a difference between participants who are able to dorsiflex at baseline compared to those that do not. To best understand who will benefit from WBV, it will be important for future studies to identify biomarkers for responders and non-responders.

4.2 Reflex Modulation

The WBV intervention was not associated with significant differences in soleus H-reflex modulation as measured by low-frequency depression. A previous study in which a single session of WBV decreased spinal reflex excitability in the soleus (Krause et al., 2016) was the basis for the hypothesis that WBV would improve soleus spinal reflex modulation in persons with spasticity. Moreover, a prior study of participants with motor-incomplete SCI who received a 12-session WBV intervention over 4 weeks found that reductions in quadriceps excitability in response to stretch (the pendulum test) persisted 6-8 days after the final WBV intervention in some participants (Ness & Field-Fote, 2009a). As with dorsiflexion, it is possible that the distribution of the WBV dose over a shorter time period was insufficient to evoke a neuroplastic effect.

5. Conclusions:

Whole body vibration applied for 9 sessions over the course of 2 weeks does not appear to have an influence on dorsiflexion during walking or soleus H-reflex that persists following the intervention. Applying WBV for shorter or longer durations did not affect the outcomes. In future studies of WBV and other forms of afferent stimulation, the timing of the effects of vibration and the distribution of the dose will be of importance, as will identifying responders- vs non-responders.

Bout Group		Sham-Stimulation Wash-In Phase		Whole Body Vibration Phase	
Short	**T1**	16 bouts per session	**T2**	8 bouts per session	**T3**
Long		8 bouts per session		16 bouts per session	

Table 3.1: Study Design. Participants were stratified to receive short- or long-bout WBV. The sham- stimulation wash-in phase (T1 to T2) consisted of 10 sessions of sham-stimulation, in which participants stood on a WBV platform for 45-seconds followed by 1-minute of seated rest for the designated bouts set by the bout group. The Whole Body Vibration phase (T2 to T3) consisted of 9 sessions of 50Hz WBV with the same stand/rest timing. The 10^{th} WBV session occurred immediately after T3 testing.

Table 3.2. Demographics

Subject ID	Sex	Age (years)	Time since injury y (m)	AIS	Neurological Injury Level	LEMS (weaker)	LEMS (stronger)	LEMS (total)	Spastic Leg
40	F	21	1 (0)	D	T11	24 (R)	25	49	R
43	M	49	29 (5)	D	C5	18 (R)	25	43	R
49	F	63	5 (8)	D	C5	21 (R)	24	45	R
53	M	45	1 (9)	D	C4	9 (L)	17	26	L
55	M	44	19 (11)	D	C2	11 (L)	25	36	L
64	M	69	2 (1)	D	C4	21 (R)	24	45	R
65	M	53	0 (6)	D	C3	25 (L)	25	50	L
67	M	60	3 (3)	D	C5	23 (L)	24	47	L
48	M	52	3 (4)	D	C4	23 (L)	23	46	L
52	M	61	2 (0)	D	C1	23 (L)	25	48	L
56	M	37	2 (6)	D	C3	13 (R)	14	27	L
60	F	29	0 (11)	D	T8	22 (R)	22	44	R
62	M	40	0 (8)	D	C4	21 (L)	25	46	L
70	F	59	4 (8)	D	C7	24 (R)	25	49	R
73	F	75	6 (11)	D	C6	14 (R)	23	37	R
74	F	61	15 (3)	D	C5	21 (L)	24	45	L

Abbreviations: AIS, American Spinal Injury Association Impairment Scale (D: Motor function is preserved below the neurological level); I Lower Extremity Motor Score; R, Right; L, Left.

Table 3.3 Sham- Stimulation vs. WBV Phase

Subject ID	Dorsiflexion during Swing ° Δ			Low-frequency Depression % Δ		
	Stim	WBV	Overall	Stim	WBV	Overall
	T2-T1	T3-T2	T3-T1	T2-T1	T3-T2	T3-T1
Short-Bout Group						
40 $^{-}$	0.17	-4.13	-3.96	-27.85	32.35	4.50
43 $^{-}$	8.45	0.78	9.23	1.31	35.09	36.41
49 $^{-}$	-0.5	3.25	2.75	-8.54	-15.30	-23.84
53 $^{+}$	-5.16	5.74	0.58	-18.82	1.89	-16.93
55 $^{-}$	0.96	-1.38	-0.42	15.38	-0.75	14.64
64 $^{+}$	-0.24	-2.86	-3.09	34.03	-25.69	8.35
65 $^{-}$	2.98	1.21	4.19	-6.04	-15.22	-21.26
67 $^{+}$	-3.96	-0.39	-4.35	28.07	-19.82	8.25
Long-Bout Group						
48 $^{-}$	-6	5.15	-0.85	70.26	-75.41	-5.15
52 $^{+}$	-4.58	5.35	0.77	7.22	25.92	33.14
56 $^{+}$	-0.87	-5.11	-5.97	-51.74	10.31	-41.43
60 $^{+}$	-0.04	-0.54	-0.58	16.24	10.91	27.16
62 $^{-}$	5.47	-2.42	3.05	-9.49	26.67	17.18
70 $^{-}$	-0.03	-1.03	-1.06	-20.15	-6.12	-26.27
73 $^{-}$	-0.42	-0.68	-1.10	17.90	17.27	35.17
74 $^{-}$	-1.35	0.18	-1.17	-10.44	0.15	-10.29

Abbreviations: Stim, Sham- Stimulation Wash-in Phase, WBV, Whole Body Vibration Phase, $^{+}$dorsiflexion at T1, $^{-}$plantarflexion at T1

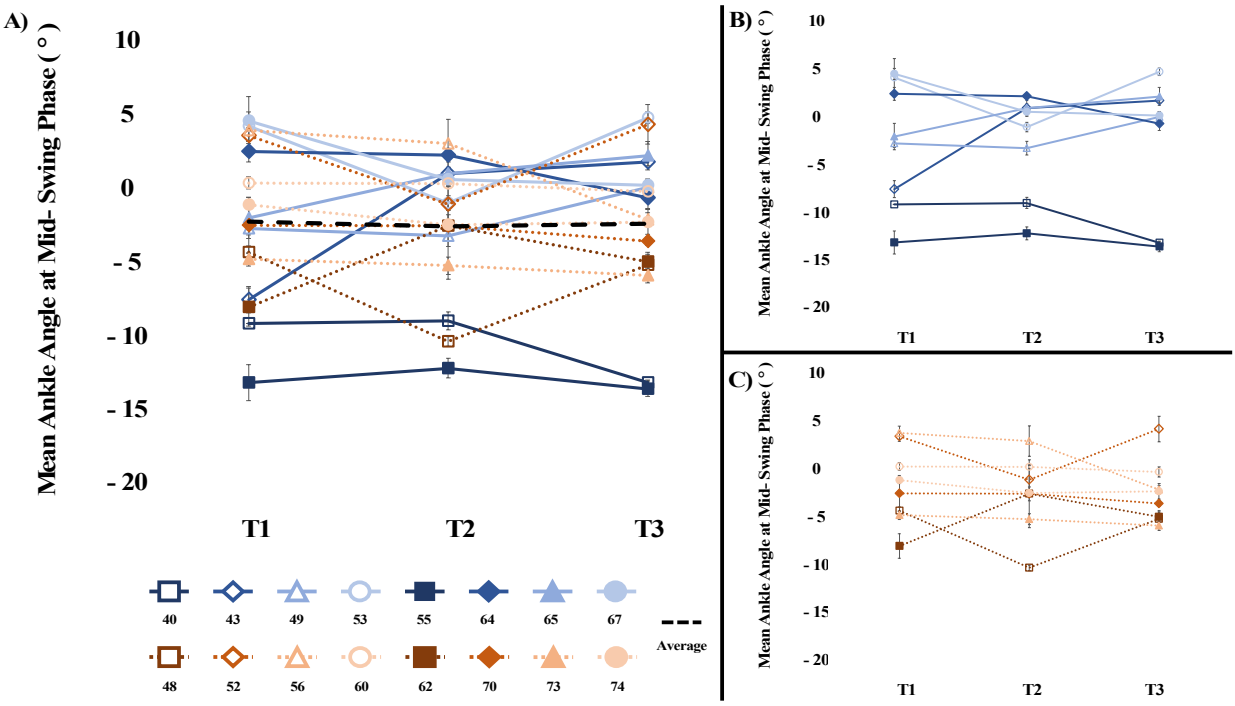

Figure 3.1: Dorsiflexion during Swing Phase (°). **A)** The average mean ankle angle at mid-swing phase of the short- and long- bout groups. **B)** Short-bout group, blue **C)** Long-bout group, orange. Positive values represent dorsiflexion, and negative values plantarflexion. T1 to T2 = sham-stimulation phase. T2 to T3 = WBV intervention phase. Error bars represent standard error of mean across walks.

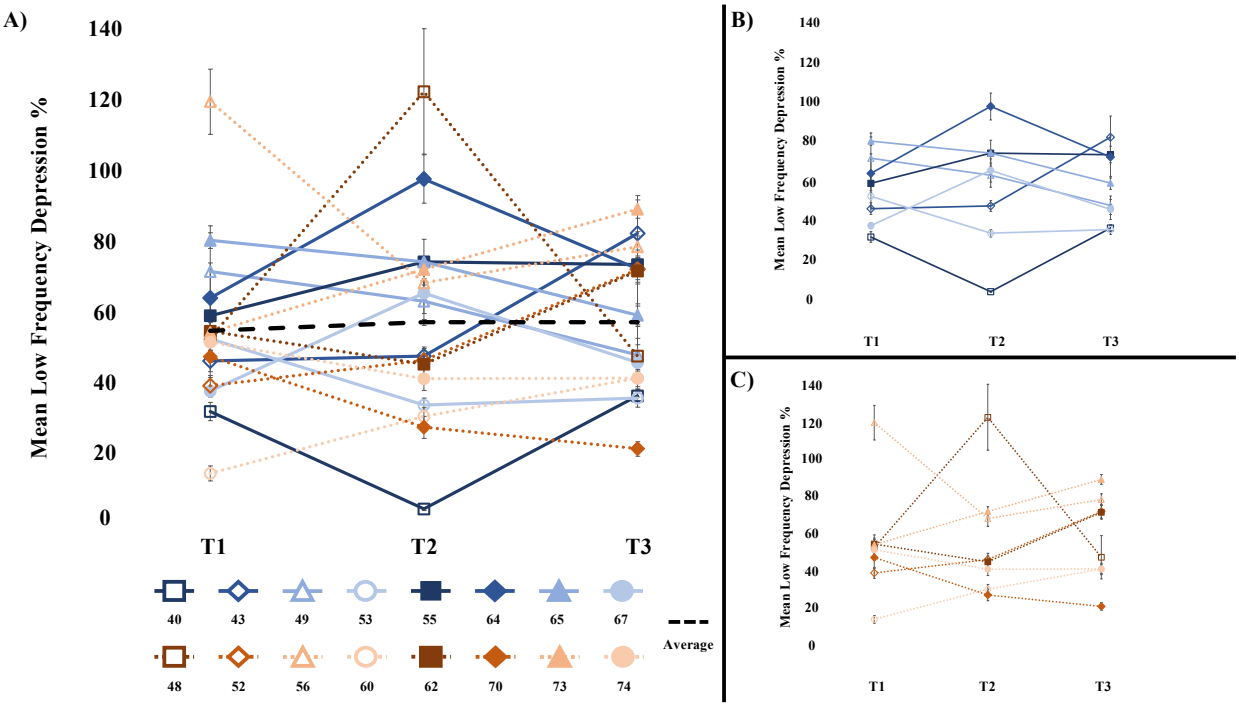

Figure 3.2: Low-frequency depression %. A) The average low-frequency depression % (Average of the 10 conditioned stimuli) / test stimulus) *100% of the short- and long- bout groups. **B)** Short-bout group, blue **C)** Long-bout group, orange. Higher percentage values indicate greater inhibition. Values lower than 100 are indicative of inhibition, while values greater that 100 are indicative of facilitation. We expected increased inhibition (lower values) to occur after WBV. T1 to T2 = sham-stimulation phase. T2 to T3 = WBV intervention phase Error bars represent standard error of mean.

Chapter 4:Assessment of dorsiflexion ability across tasks in persons with subacute SCI after combined locomotor training and transcutaneous spinal stimulation

1. Introduction:

Walking is one of the top rehabilitation priorities after spinal cord injury (SCI) (Ditunno et al., 2008). After SCI, limitations in the ability to achieve adequate dorsiflexion can contribute to impaired ability to achieve foot clearance. This debilitation, known as foot drop, interferes with walking ability and increases fall risk (Kemoun et al., 2002). Since the dorsiflexors are the lower extremity muscles most highly influenced by supraspinal input (Capaday et al., 1999; Schubert et al., 1997), damage to the corticospinal tract after SCI has a considerable impact. Although corticospinal tract descending drive influences dorsiflexion during isolated joint movement and walking (Capaday et al., 1999), spinal pattern generating circuits also strongly contribute to the latter (Calancie et al., 1994; Minassian et al., 2017). Furthermore, the additional proprioceptive input during weight-bearing stepping compared to isolated joint movement increases the activation of motor neuron pools responsible for dorsiflexion (Maegele et al., 2002). Taken together, these processes would seem to promote greater ability to activate dorsiflexors during walking compared to isolated volitional ankle movements.

In addition to impaired ability to activate dorsiflexors, damage to the spinal cord results in other challenges that further complicate ankle control, including the involuntary muscle contractions and stiffness associated with spasticity in the plantar-flexors (Manella et al., 2013). During walking, involuntary activation of the plantar-flexors during terminal stance may impede ability to activate the dorsiflexors (Yang et al., 1991). Consequently, the presence of plantar-flexor spasticity would seem likely to be associated with lower ability to activate the dorsiflexors during walking, compared to isolated volitional movement.

Transcutaneous spinal stimulation (TSS) activates the dorsal root fibers carrying afferent information, which influences both volitional and reflex motor output (Hofstoetter et al., 2015). Prior studies have provided evidence for the immediate effect of TSS on plantar-flexor spasticity and

dorsiflexor activation. During 30 Hz frequency of TSS in persons with incomplete SCI, there was an immediate increase in maximum active range of motion (AROM) during a rhythmic ankle task (Meyer et al., 2020). Additionally, in persons with multiple sclerosis, 50 Hz frequency of TSS improved walking outcomes 2 hours post-stimulation and spasticity outcomes both 2 and 24 hours post-stimulation (Hofstoetter et al., 2021). To better understand the temporal persistence of TSS in persons with SCI, there is a need for studies assessing the effects of multiple applications of TSS in conjunction with task-specific training (Meyer et al., 2020).

Task-specific training is founded on theories of Hebbian learning (Kandel & Hawkins, 1992), wherein specificity and repetition are thought to be essential for improvements in performance (Hubbard et al., 2009). Therefore, to improve locomotor outcomes therapists have utilized locomotor training (LT) emphasizing repetitive stepping practice to improve gait quality in persons with SCI (Nooijen et al., 2009). Unfortunately, most persons with SCI do not receive the number of repetitions needed to experience the optimal effects of this rehabilitation intervention (Sandler et al., 2017). To address this challenge, interventions that prime the nervous system have value for enhancing the efficacy of training (Field-Fote, 2015). Although TSS has been shown to improve walking outcomes, such as speed and endurance (Hofstoetter et al., 2021), the basis for these improvements has not been explored. One possibility is that it contributes to improved ankle control (Meyer et al., 2020), therefore allowing for improved foot clearance. In the development of TSS interventions to improve functional outcomes, it is important to understand how it influences both voluntary and involuntary muscle activation, and how it may contribute to the ability to achieve adequate dorsiflexion (Hope et al., 2020).

Beyond examining the influence of TSS on ankle control, it is important to understand whether there is greater preservation of dorsiflexion as part of the pattern of walking compared to during an isolated, volitional motor task. Although previous studies in persons with SCI have attempted to examine the relationship between volitional activation of the dorsiflexors during a task and walking outcomes (Adrian et al., 2022; Barthelemy et al., 2013; Thompson et al., 2019), the contribution of ankle

dorsiflexors during swing phase in these improvements has yet to be identified. For instance, in a study that examined the relationship between corticospinal tract descending drive to the tibialis anterior and dorsiflexion during swing phase, toe clearance and ankle excursion were calculated (Barthelemy et al., 2013). However, toe clearance can be influenced by hip and knee joint changes and ankle excursion during swing phase can be biased due to increased plantar-flexion at the initiation of swing. To best understand the role of dorsiflexor activation during swing phase and how it is impacted by noninvasive stimulation, peak dorsiflexion during swing phase must be analyzed.

Since the ability to activate the dorsiflexors in isolation may or may not be reflected in the ability to achieve dorsiflexion during walking, it is important to test dorsiflexor control under both conditions. In addition, there is value in understanding the relationship between plantar-flexor spasticity and dorsiflexor control. The aim of the current study was to determine whether LT combined with TSS is associated with a persistent effect on dorsiflexion during walking and dorsiflexor AROM in persons with subacute motor-incomplete SCI beyond that observed with LT alone. Additionally, the relationship between plantar-flexor spasticity and the ability to dorsiflex across the different tasks (walking and volitional control) was assessed. Due to the role of CPG in walking and because LT is being utilized in this study, we predicted that dorsiflexion during walking would show greater improvements than dorsiflexion during the volitional task.

2. Materials and Methods:

This study was carried out with the ethics approval from the Shepherd Center Research Review Committee. All participants provided written informed consent prior to study enrollment in accordance with the Declaration of Helsinki and the study was conducted in accordance with the Health Insurance Portability and Accountability Act guidelines. The data used to address the questions of relevance for control of ankle dorsiflexors is a subset of data collected as part of a larger study (Estes et al., 2021), which was registered with clinicaltrials.gov (NCT03240601).

2.1 Participants

Individuals were eligible for participation if they met the following inclusion criteria: 16-65 years of age, 2 - 6 months since time of spinal cord injury, qualify for participation in a clinical LT program as determined by their physical therapist, and able to walk 10 meters without the use of ankle-foot orthosis. Individuals were excluded for the following reasons: neurological level of injury at or below T12, progressive or potentially progressive spinal lesions, history of cardiovascular irregularities, difficulty following instructions, orthopedic limitations, women who were pregnant or had reason to believe may become pregnant, persons who had implanted stimulators/electronic devices of any type, and persons with an active infection of any type.

2.2 Study Design

This was a pragmatic clinical trial that used a randomized, wash-in, sham-control design with 4 consecutive weeks of LT. The LT component was directed by physical therapists as part of usual care. Participants were randomized to either an intervention LT+TSS group or a control LT+TSS_{Sham} group. During the first 2 weeks (wash-in phase), all participants received LT 3 days per week. During the second 2 weeks (intervention phase), participants in the LT+TSS group received LT augmented by TSS 3 days per week; participants in the LT+TSS_{Sham} group received LT combined with sham TSS 3 days per week. Outcome assessments for ankle angle during a dorsiflexor activation task, walking, and spasticity were conducted at the beginning and end (T1, T2, respectively) of wash-in phase, and at the beginning and end (T3, T4, respectively) of the intervention phase.

2.3 Intervention

2.3.1 Locomotor Training (LT)

As a pragmatic trial, the LT strategy used for each participant was determined by the physical therapist in accordance with standard clinical practice and ranged from treadmill-based training (with or without body weight support, and with or without manual or robotic assistance [Lokomat, Hocoma,

Volketswil, Switzerland]) to overground LT (with or without body weight support, and with or without manual assistance).

2.3.2 Transcutaneous Spinal Stimulation (TSS)

Electrical stimulation was applied using a portable, clinical electrotherapy device (Empi Continuum, DJO Global, Vista, CA, USA). The stimulating electrode (5 cm round electrode) was placed over vertebral levels T11/T12 (identified via manual palpation); the reference electrode (10 cm x 15 cm butterfly electrode) was placed over the umbilicus. For participants randomized to the LT+TSS group, biphasic stimulation was delivered at 50 Hz. Target stimulation intensity was individualized during each session at an intensity that produced participant-reported paresthesia of the lower legs and feet or to the highest intensity the participant could tolerate. Target intensity was subthreshold for observable lower extremity muscle activation as indicated by the absence of visible or palpable muscle activation. Stimulation time was standardized to 30 minutes in duration, and was delivered at the target stimulation intensity concomitantly with LT. Following 30 minutes of stimulation, the intensity was ramped down, the stimulation unit was turned off, the leads were disconnected, and the LT continued as directed.

2.3.3 Sham-control Stimulation

The sham-control was designed to control for placebo effects associated with the TSS intervention. The stimulator, electrodes, and electrode positions used for the LT+TSS_{Sham} group was the same as described above for the LT+TSS group. Participants were instructed that the stimulation would be reduced to an intensity that they could not feel. The intensity of electrical stimulation was then briefly ramped up to a level at which the participants reported perceiving the stimulation, ramped down to subsensory threshold, and then turned off for the remainder of the intervention. The stimulator and electrodes remained attached to the participant for 30 minutes of the LT session, comparable to the active TSS intervention. After 30 minutes, the stimulator unit was disconnected from the electrode leads.

2.4 Outcome Measures

All measures described below were captured from the more spastic leg as determined by higher number of clonus oscillations at T1.

2.4.1 Dorsiflexion during Walking

To assess change in swing phase dorsiflexion during walking, we quantified peak ankle angle based on kinematic data captured using inertial measurement unit sensors (XSENS MVN, Xsens Technologies BV, Enschede, The Netherlands). Inertial measurement unit sensors were strapped bilaterally to lower extremities (attached to the pelvis at the center of the back at the height of the anterior superior iliac spine, and bilaterally to the middle of the lateral thighs, tibias, and dorsum of the feet inside shoe laces) according to manufacturer guidelines to capture ankle joint angles using inertial motion capture software (XSENS). Calibrated angles were verified during standing with the hip and knee in full extension, and the ankle in neutral prior to starting the test. Participants walked overground along a 10-meter walkway following the instruction to walk as quickly and safely as possible. This test was performed 3 times with a 2-minute rest interval between trials. For each walk, the middle 50 percent of steps for the tested foot was analyzed to remove any impact of acceleration and deceleration. Peak sagittal ankle angles at mid-swing were extracted from the sensor data, where positive angles indicated dorsiflexion and negative angles indicated plantarflexion. Based on previous data from treadmill walking in persons with stroke, the minimal detectable change for peak ankle angle during swing phase is 4.9 degrees (Kesar et al., 2011); this was used as a benchmark in the current study.

2.4.2 Dorsiflexor Activation Task

To assess the change in ability to activate the dorsiflexor muscles, we assessed both AROM, and electromyographic (EMG) activity in the tibialis anterior muscle during a dorsiflexor activation task. Participants were positioned reclined on an adjustable height mat table with both legs extended and shoes removed. Sensor placement was as described above for walking, but with shoes off (XSENS). EMG recording electrodes (Motion Lab Systems, Baton Rogue, LA) were placed over the muscle belly of the

tibialis anterior midway between the knee and ankle joint. EMG data signals were captured at a 1000Hz sampling rate using commercial software (Spike CED, Cambridge Electronics Design, UK).

Participants were instructed to pull their toes up toward their head as hard and fast as they could at the onset of a 5-second auditory tone and to maintain that contraction until the tone stopped. This test was performed 3 times with a 30-second rest interval between trials. If background EMG indicated the tibialis anterior muscle was not at rest before or after the tone, or if the dorsiflexion movement elicited ankle clonus, then that trial was discarded, and the test was repeated. EMG data related to the time between the start and end of the auditory tone were processed offline using customized, commercial software (Spike CED, Cambridge Electronics Design, UK) with a root mean square (RMS) filter of 8ms (Manella et al., 2013). AROM and average RMS amplitude of EMG were both analyzed offline using customized MATLAB software (MATLAB, Mathworks).

2.4.3 Ankle Clonus Drop Test

The standardized methodology for the ankle clonus drop test was as described previously (Estes et al., 2021). The spasticity data analyzed for the current study is a subset of that previously reported and includes data only from those participants who could walk without the use of ankle orthoses with the intent to address questions about the relationship between spasticity and ankle control. Briefly, participants sat upright with back support on the edge of a mat table, with shoes removed and socks left on with inertial measurement sensor (XSENS) placements as described above. The ball of one foot was positioned on the edge of a platform (10 cm height). The mat height was adjusted to ensure that the hip, knee, and ankle joints were at 90-degree angles. The participants' leg was lifted from beneath the knee until it contacted a T-bar positioned 10 cm above the resting position of the knee. The examiner quickly released the leg allowing the forefoot to impact the edge of the platform. Responses in each ankle were tested 3 times. The number of clonus oscillations during 10 seconds in each trial was counted offline, and the average number of oscillations for the 3 trials of each test session was used for analysis. Ankle joint oscillations were analyzed off-line using customized MATLAB software (MATLAB, Mathworks, Natick,

MA, USA). A number of oscillations equating to 4 or greater is indicative of pathological ankle clonus (Koelman et al., 1993).

2.5 Data Analysis

Data were analyzed using SPSS (version 26-28; SPSS Inc., Chicago, IL, USA). Descriptive statistics (mean [standard deviation]) of the measures of interest were calculated for each group. Because the small sample precluded the use of interferential statistics for between-groups comparisons, and since it has been asserted that effect sizes are more meaningful for clinical interpretation than p-values (Borenstein, 1997), we based comparisons on within-group effect sizes for each measure. Effect size was computed using Cohen's *d*, and outcomes were categorized as small (0.14), medium (0.31) and large (0.55) effects based on interpretations for rehabilitation data (Kinney et al., 2020). Spearman's rank correlations were used to assess associations between measures. To assess the overall effect of 4 weeks of LT on the measures of interest, data were pooled across phases and groups and analyzed using Wilcoxon signed rank tests and effect sizes were calculated and interpreted as described above.

3. Results:

3.1 Demographics

Ten participants (1 Female) met the inclusion criteria for this study (**Table 4.1**). Of these participants, 6 were randomized to the LT+TSS group and 4 were randomized to the LT+TSS_{Sham} group. The mean age was 43.67(20.19) years with an average time of 96(57.03) days since injury for the LT+TSS group. In the LT+TSS_{Sham} group, the mean age was 36.75(11.9) years with an average time of 92.5(22.87) days since injury.

3.2 Dorsiflexion during Walking

Dorsiflexion outcomes related to walking (peak swing phase dorsiflexion angle) and the dorsiflexor activation task (AROM, EMG) for each group can be found in **Table 4.2**.

In the LT+TSS group there was no increase in peak ankle angle during swing phase in either the wash-in or the intervention phase (effect sizes <0.14). Conversely, in the LT+TSS_{Sham} group there was increased peak ankle angle during the wash-in phase but a decreased ankle angle during the intervention phase, with medium and small effect sizes, respectively. Only one participant (in the LT+TSS group) had a peak angle increase above 4.9 degrees (P18 during wash-in; **Figure 4.1**).

3.3 Dorsiflexor Activation Task

For the dorsiflexor activation task, there was an increase in AROM during the wash-in phase in the LT+TSS group, with a medium effect size. However, there was no effect on AROM observed during the intervention phase. Likewise, in the LT+TSS_{Sham} group there was increased AROM during the wash-in phase with a small effect size and no change during the intervention phase (**Figure 4.2**).

The LT+TSS group had a decrease in dorsiflexor EMG amplitude during both the wash-in and intervention phases, with small effect sizes. In the LT+TSS_{Sham} group there was an increase in dorsiflexor EMG during wash-in phase with a medium effect size, and no change during the intervention phase.

3.4 Overall effects of locomotor training on ankle-related outcomes and relationships among measures

As equivalent effects were observed in both groups during the intervention phase, suggesting there was no persistent effect of TSS, data were pooled across groups and across study phases (T1 – T4) to assess the overall effects of 4 weeks of LT. Average peak ankle angle during the swing phase of gait was 0.33 (5.1) degrees at baseline and increased to 2.18 (5.7) after 4 weeks of LT with a medium effect size (Z = - 0.97, p = 0.333, d = 0.34). Two individuals from the study had a change in peak ankle angle that met the minimal detectable change of 4.9 degrees (P09: 7.86 degrees; P18: 9.63 degrees). AROM during the dorsiflexor activation task increased with a medium effect size from 22.04 (16.40) degrees at baseline to 27.03 (14.22) after 4 weeks of LT (Z = -1.48, p = 0.139, d = 0.33). Active dorsiflexor EMG amplitude was 40.89 (30.66) µV at baseline, increasing to 48.13 (26.05) µV at T4 with a small effect size (Z = -1.07, p = 0.285, d = 0.25) The number of ankle clonus oscillations decreased from 11.37 (11.18)

beats at T1 to 9.17 (11.17) at T4 with a small effect size (Z = -0.28, p = 0.778 , d = -0.2). Additionally, 5 out of 10 individuals (P04: 15.33 average beats; P05: 4.67 average beats; P06: 32 average beats; P13: 24.33; P18: 22.33 average beats) had pathological clonus at T1, but only 3 of those individuals (P06, P13, and P18) remained in the pathological category of clonus at T4 (P04: 3.67 average beats; P05: 2.67 average beats; P06: 32.33 average beats; P13: 8.67; P18: 27.67 average beats). However, in one participant there was a small increase in the number of beats of clonus that was sufficient to change their classification from not having pathological clonus at T1 (P15: 3.33 average beats) to being categorized as having clonus at T4 (P15: 4.33).

There were large significant correlations between AROM in the dorsiflexor activation task and peak ankle angle achieved during swing phase across all timepoints (T1, $\rho = 0.64$, $p = 0.024$, T2, $\rho = 0.82$, $p = 0.002$, T3, $\rho = 0.87$, $p < 0.001$, T4, $\rho = 0.82$, $p = 0.002$; Figure 3). Additionally, the change (T4 – T1) in ankle clonus oscillations, had a strong positive association with change in active dorsiflexor EMG amplitude ($\rho = 0.78$, $p = 0.004$) but not with AROM ($\rho = 0.36$, $p = 0.151$) or peak ankle angle during swing phase ($\rho = 0.19$, $p = 0.305$).

4. Discussion:

4.1 Dorsiflexion during Walking

Due to the importance of dorsiflexor control during swing phase of walking and the observation of improved walking speed and distance in the LT+TSS group in the larger study of which these data were a subset (Estes et al., 2021), we predicted that combined LT+TSS would improve dorsiflexion during swing phase. However, training with combined LT and TSS did not have a persistent impact on dorsiflexion during swing phase beyond that observed for LT, as there was no effect for increase in peak ankle angle during either phase in the LT+TSS group. In a prior report, during stimulation the immediate effects of TSS on ankle range of motion during walking were variable, but 3 of 6 participants demonstrated increased ankle range of motion in at least one leg (Meyer et al., 2020). Given that TSS has

been associated with both increased joint range of motion during walking (Hofstoetter et al., 2015) and during volitional tasks (Meyer et al., 2020), and since there is an association between increased foot clearance and increased walking speed (Barthelemy et al., 2010), it seemed reasonable that the improvements in walking speed and distance with TSS stimulation may be due to enhanced ability to activate dorsiflexors. However, our data did not support that hypothesis.

Based on the findings of these analyses it seems likely that the increase in walking outcomes exhibited in prior studies may be due to changes in other joints important for foot clearance during walking. For example, in persons with stroke those with reduced ability to dorsiflex the ankle had an increase in peak hip flexion during swing phase, resulting in a negative correlation between hip and ankle flexion during swing phase (Roche et al., 2015). Conversely, in an operant conditioning study in persons with SCI, an increase in tibialis anterior corticospinal tract descending drive was associated with increased peak ankle dorsiflexion and improved walking outcomes, but not increased knee or hip flexion (Thompson et al., 2019). However, this kinematic peak joint angle was calculated over the entire step cycle making it unclear whether the increase was specific to swing phase. Therefore, there is still a possibility of a phase-dependent association between increased hip and knee flexion with decreased ankle dorsiflexion during swing phase in people with SCI that should be examined in future studies.

4.2 Dorsiflexor Activation Task

In contrast with immediate effects on volitional dorsiflexion observed during TSS (Meyer 2020), training that combined LT and TSS did not have a persistent impact on dorsiflexion AROM. This was indicated by medium and small effect size observed in both groups during the wash-in phase, but no effect during the intervention phase for the TSS group (or the TSS_{Sham} group). We predicted that training with 50Hz TSS would have a persistent effect based on prior evidence that the influence of TSS motor output and spasticity were temporally persistent, for at least 2 hours and up to 24 hours, respectively, in persons with multiple sclerosis (Hofstoetter et al., 2021). Considering these findings in the context of prior studies in persons with SCI, it would appear that TSS has an immediate effect on ankle dorsiflexion

during application of the stimulation (Meyer et al 2020), but these effects do not exhibit temporal persistence.

4.3 Overall effects of locomotor training on ankle-related outcomes

Considering the task-specificity of LT on walking outcomes and the role of central pattern generator circuits in walking, we expected there to be a stronger influence of LT on dorsiflexion during swing phase than on dorsiflexion during a volitional task. However, we found the effects 4 weeks of locomotor training on peak ankle angle during swing phase of walking and AROM in the dorsiflexor task were equivalent, with an overall medium effect for both. In fact, there was a strong positive correlation between peak ankle angle during swing phase and AROM during the dorsiflexor activation task. These findings point to the relationship of dorsiflexion during walking, which occurs without conscious volitional effort and has contributions from spinal central pattern generating circuits (Calancie et al., 1994), and volitional isolated dorsiflexion, which relies on conscious effort to engage direct cortical activation (Capaday et al., 1999; Dobkin et al., 2004). There has been recent evidence that corticospinal tract descending drive during a complex ankle control task is associated with walking outcomes (Adrian et al., 2022). Additionally, although dorsiflexors do not require conscious input during walking, there is evidence that descending supraspinal drive influences walking (Barthelemy et al., 2013; Dobkin et al., 2004). Therefore, perhaps the degree of corticospinal tract descending drive to the dorsiflexors is what is driving the strong relationship we observed in our study.

The average peak dorsiflexion angle during swing phase across participants was around 0 degrees (neutral), which is comparable to a non-injured individual (Gates et al., 2012). Some individuals in our study had peak dorsiflexion angles that were above neutral, as has been observed in another study of participants with motor-incomplete SCI (Thompson et al., 2019). In fact, 2 participants (P09 and P18) exhibited an increase in peak ankle angle during swing phase above the minimal detectable change of 4.9 degrees (Kesar et al., 2011). Although on average the degree change was small, even a small increase in dorsiflexion during swing phase can enable toe clearance and decrease fall risk. Therefore, there is a need

to determine the minimal clinical important change for dorsiflexor activation during walking. As locomotor training is currently the standard of care for individuals with acute/subacute SCI who have potential to regain walking ability, it is not possible to know whether these improvements would have occurred in the absence of this training in these participants.

Unexpectedly, after 4 weeks of locomotor training there was a strong positive association between ankle clonus oscillations, our indicator of reflex responsiveness to stretch of the plantar-flexors, and dorsiflexor EMG amplitudes during volitional activation. Theoretically, increased ability to activate the tibialis anterior activity would be associated with increased reciprocal inhibition to the plantar-flexors and therefore decreased reflex activation of the soleus. However, in some persons with SCI, remodeling of spinal circuits results in a reversal of reciprocal inhibition to reciprocal facilitation (Crone et al., 2003; Mirbagheri et al., 2014). Therefore, our results may be due to this phenomenon.

While we selected 50Hz TSS because prior work suggests it both improves motor output and decreases spasticity (Hofstoetter et al., 2021), more recent evidence from studies using 30Hz stimulation suggest this lower frequency may also be effective at influencing our outcomes of interest. Perhaps the effects of TSS in our study may have been more beneficial if 30 Hz was utilized, as this has been shown to have neuromodulatory effects on voluntary locomotor activity ((Hofstoetter et al., 2015; Meyer et al., 2020). However in a direct comparison of the effects of 30 Hz vs 50 Hz TSS on locomotor-related outcomes, there was no significant difference between 30 Hz and 50 Hz TSS (Meyer et al., 2020).

4.4 Limitations

The number of participants who were able to walk without the use of ankle orthotics was small, resulting in a small sample size. In addition, participants' ability to volitionally activate the dorsiflexors may have not been fully captured as the supine position with knees extended requires the participant to overcome tension in the gastrocnemius. Further, this position may facilitate an extensor response in persons with spasticity.

5. Conclusions:

The current study does not provide evidence of a persistent effect of combined TSS and LT on volitional dorsiflexion or dorsiflexion during the swing phase of walking, as there were no differences between the group that did and the group that did not receive TSS. However, after 4 weeks of locomotor training, improvements were observed in all outcome measures. Our findings support the relationship of dorsiflexion during walking and volitional isolated dorsiflexion, which both have shared corticospinal mechanisms, but the latter is influenced by central pattern generators. Factors other than enhanced dorsiflexor activation are likely responsible for improved walking outcomes associated with TSS observed in other studies.

Table 4.1 Demographics

Subject ID	Sex	Age (years)	Time since injury (days)	AIS	Neurological Injury Level	LE (tested)	Clonus (tested)	Group
P04	F	53	36	D	C2	L	15.33	**LT+TSS**
P05	M	56	84	D	C4	R	2.67	**LT+TSS**
P09	M	18	83	D	C7	R	3.00	**LT+TSS**
P15	M	54	141	D	C5	R	3.33	**LT+TSS**
P16	M	63	185	D	C1	R	3.00	**LT+TSS**
P18	M	18	47	D	C5	L	22.33	**LT+TSS**
P02	M	43	80	C	C4	R	2.67	**LT+TSS$_{Sham}$**
P06	M	37	103	C	C3	L	32.00	**LT+TSS$_{Sham}$**
P08	M	47	119	D	C2	L	3.00	**LT+TSS$_{Sham}$**
P13	M	20	68	D	C4	R	24.33	**LT+TSS$_{Sham}$**

Abbreviations: AIS, American Spinal Injury Association Impairment Scale; LE, Lower Extremity; R, Right; L, Left.

Table 4.2 Outcomes

	Wash-in Phase				Intervention Phase			
	T1	**T2**	**Difference**	**Effect size**	**T3**	**T4**	**Difference**	**Effect size**
Peak Dorsiflexion during Swing Phase (°)								
LT+TSS	0.76 (5.23)	0.96 (5.21)	0.20 (4.41)	0.04	2.93 (5.67)	3.36 (6.20)	0.43 (2.92)	0.07
LT+TSS$_{Sham}$	-0.31 (5.63)	1.34 (4.75)	1.65 (3.83)	0.32	1.85 (5.12)	0.41 (5.14)	-1.44 (2.52)	-0.28
Ankle Volitional Range during Dorsiflexion Task (°)								
LT+TSS	25.32 (18.41)	30.45 (12.97)	5.13 (8.49)	0.32	29.24 (12.85)	30.30 (13.61)	1.06 (5.68)	0.08
LT+TSS$_{Sham}$	17.12 (13.71)	21.17 (21.64)	4.04 (9.60)	0.22	21.68 (15.99)	22.13 (15.62)	0.45 (10.56)	0.03
EMG during Volitional Task (μv)								
LT+TSS	54.49 (29.73)	49.48 (13.57)	-5.01 (21.01)	-0.22	60.26 (32.59)	52.48 (29.15)	-7.78 (19.75)	-0.25
LT+TSS$_{Sham}$	20.48 (20.53)	31.15 (31.31)	10.67 (14.40)	0.4	43.65 (29.86)	41.60 (24.42)	-2.05 (22.51)	-0.08

Table 4.2: Outcomes. The measures of interest are displayed above as mean(standard deviation). Effect sizes were calculated using Cohen's *d*.

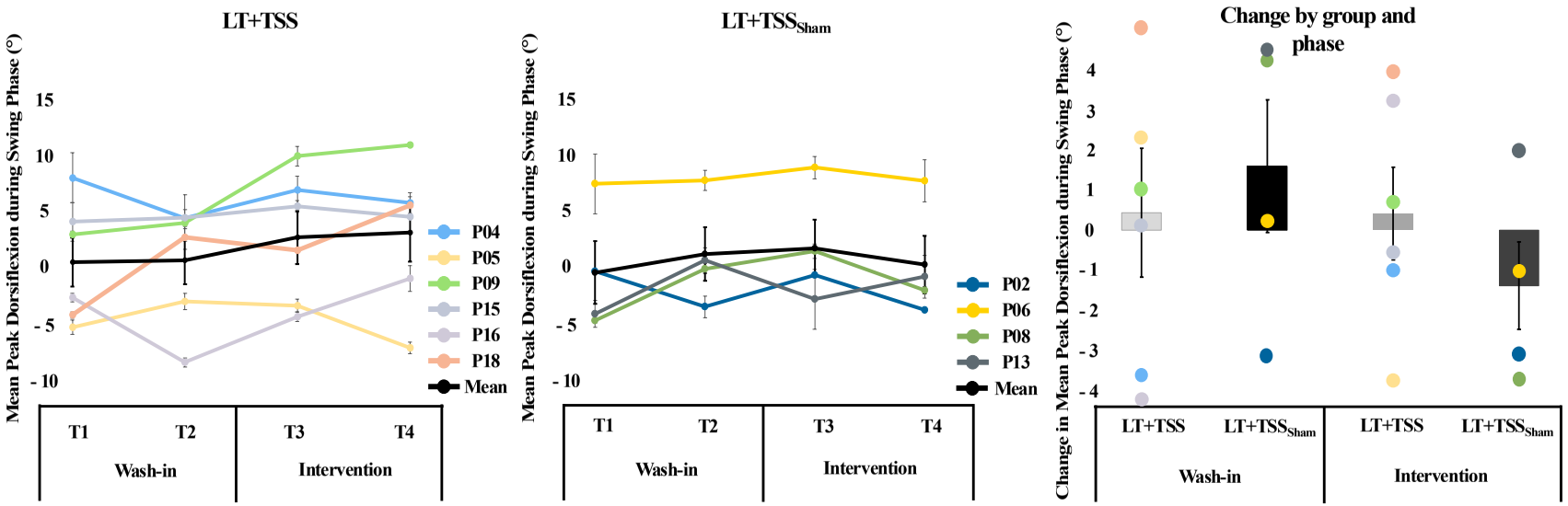

Figure 4.1: Mean Ankle Angle at Mid-Swing Phase. The average peak ankle angle during swing phase in the more spastic leg in individuals in the LT+TSS group (left) and LT+TSS$_{Sham}$ (center). Data for individual participants are depicted in color, while the mean is depicted with the bold black line. The change in ankle angle during swing phase calculated at the start and end of the wash-in (T1 to T2) and intervention (T3 to T4) phase in each group is depicted in the bar graph (right). Error bars represent standard error of mean.

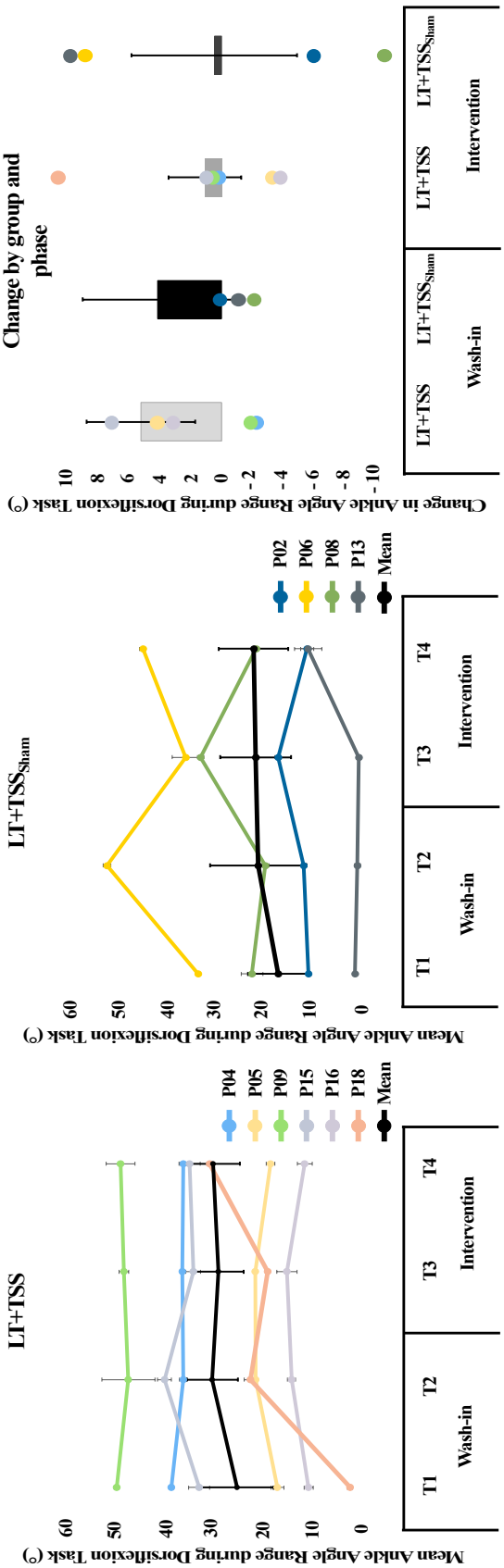

Figure 4.2: Mean Ankle Angle Range during Dorsiflexion Task. The average ankle angle during the dorsiflexion task in the more spastic leg in individuals in the LT+TSS group(left) and LT+TSS$_{Sham}$ group (center). Data for individual participants are depicted in color, while the mean is depicted with the bold black line. The change in ankle angle during the dorsiflexion task calculated at the start and end of the wash-in (T1 to T2) and intervention (T3 to T4) phase in each group is depicted in the bar graph (right). For the bar graph positive values indicate the change was toward more dorsiflexion, and negative values toward more plantarflexion. Error bars represent standard error of mean.

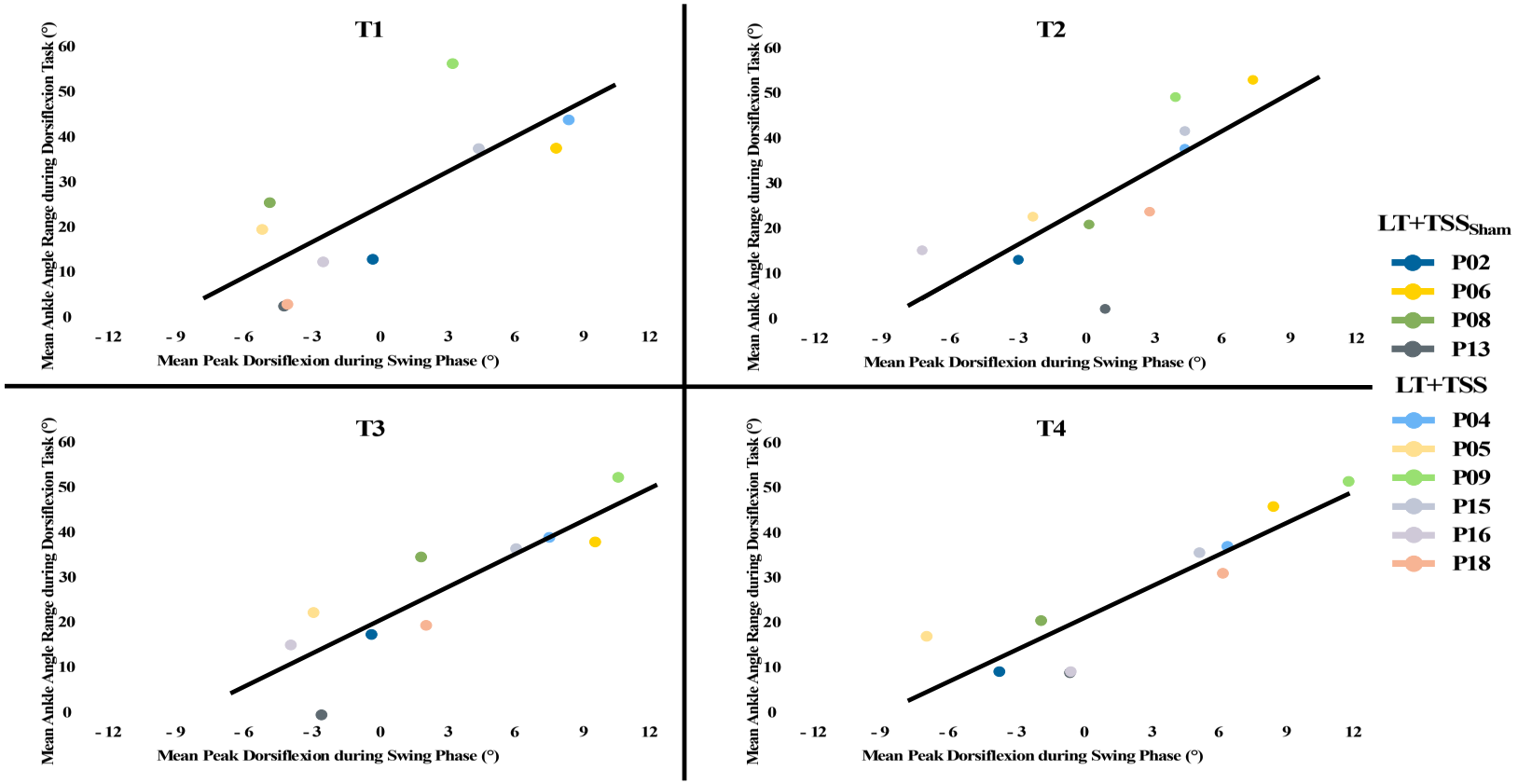

Figure 4.3: Relationship between peak ankle angle at mid-swing phase of walking and ankle angle range during dorsiflexion task. There was a strong significant correlation between dorsiflexion range of motion in the volitional ankle control task and peak dorsiflexion angle achieved during swing phase across all tests.

Chapter 5: Implications and future directions of neuromodulation techniques targeting neurophysiological mechanisms of dorsiflexor control after SCI.

CHAPTER 2: RELATIONSHIP BETWEEN CORTICOSPINAL DESCENDING DRIVE AND SPINAL REFLEX CIRCUITRY IN DORSIFLEXOR CONTROL AND PLANTAR-FLEXOR SPASTICITY

The purpose of the Chapter 2 study was to synthesize what is known about the contribution of corticospinal tract (CST) descending drive and spinal reflex circuit (SRC) modulation to disrupted ankle control after spinal cord injury (SCI) (Hope et al., 2020). Although there was a wide range of measures used across studies, there was a relationship between measures of SRC modulation and volitional ankle control (Manella et al., 2013; Piazza et al., 2016; Yamaguchi et al., 2016). The existence of this relationship across measures such as tibialis anterior strength (Piazza et al., 2016) and performance on an ankle tapping task (Yamaguchi et al., 2016) further supports the importance of decreasing excitability in the plantar-flexor SRC to increase volitional dorsiflexor control. Conversely, there was mixed evidence for the relationship between SRC excitability and plantar-flexor spasticity. This contrasting evidence may be due to the variability in both measures of SRC excitability and plantar-flexor spasticity (Adams & Hicks, 2011; Downes et al., 1995; Faist et al., 1994; Manella & Field-Fote, 2013; Manella et al., 2013, 2017; Murillo et al., 2011; Smith et al., 2015). There was a relationship between CST transmission and volitional ankle control in all studies captured (Barthelemy et al., 2013; Barthelemy et al., 2010; Labruyere et al., 2013; Wirth et al., 2008a, 2008b, 2008c, 2008d). However, at the time of publication of our scoping review, no study had assessed the relationship of CST descending drive and plantar-flexor spasticity. Since this time, a publication established a relationship between the presence of a motor evoked potential, a measure of CST descending drive, and the existence of spasticity in persons with complete SCI (Sangari et al., 2019). Overall, there is evidence of an association between neurophysiological excitability with volitional ankle control and spasticity after SCI. Future studies with a

comprehensive battery of neurophysiological assessments that examine both CST and SRC excitability in relation to the different aspects of dorsiflexor control would be beneficial for pinpointing which underlying neurophysiological mechanism is the optimal target for increasing control of dorsiflexors.

CHAPTER 3: IMPACT OF ROBUST AFFERENT STIMULATION ON DORSIFLEXION DURING SWING PHASE AND SPINAL REFLEX MODULATION

In Chapter 3, the objective was to determine if there were persistent effects of different doses of robust noninvasive afferent stimulation, in the form of whole body vibration (WBV), on dorsiflexion during swing phase of walking and plantar-flexor spinal reflex modulation in persons with SCI. Contrary to previous evidence that a single session of WBV decreased soleus SRC excitability (Krause et al., 2016) and of the persistent effect of WBV on walking outcomes (Ness & Field-Fote, 2009b), there was no persistent impact of the dose of WBV or overall effect of WBV on outcomes in our study. However, there were small, but insignificant, gains in dorsiflexion during swing phase in both people who were and were not able to dorsiflex at the beginning of the study. Therefore, although the impact may be small and not persistent, there may still be a benefit of using WBV to improve immediate dorsiflexor control in persons with SCI. In future studies, it will be important to determine the timing of the effect, optimal dose distribution, and the differences between responders and non-responders to WBV. It would also be beneficial to assess the impact of WBV on nonmonosynaptic stretch reflexes as they also impact spasticity (Jankowska & Hammar, 2002). Due to previous evidence of the antispasmodic effects of a noradrenaline and dopamine precursor that acts on group II afferents and not group I in persons with SCI (Eriksson et al., 1996),it is possible that the antispasmodic effects observed after WBV could also be due to its effects on group II afferents.

CHAPTER 4: PERSISTENT EFFECT OF COMBINED LOCOMOTOR TRAINING AND TRANSCUTANEOUS SPINAL STIMULATION ON DORSIFLEXION ACROSS TASKS IN PERSONS WITH SPASTICITY

Finally, in Chapter 4, we wanted to know if there was a persistent impact of combined locomotor training (LT) and transcutaneous spinal stimulation (TSS) on dorsiflexion during both the swing phase of walking and a volitional task in participants with SCI. Previous studies provide evidence of increased volitional control of dorsiflexors (Meyer et al., 2020) and improved walking outcomes after TSS (Hofstoetter et al., 2021). However, in our study, there was no persistent effect of TSS on dorsiflexion during walking or the volitional task. We also expected for LT to have a greater impact on dorsiflexion during walking compared to the volitional activation task, based on the theory of task-specific practice (Hubbard et al., 2009). However, we observed a moderate persistent effect of 4 weeks of LT on increased dorsiflexion during both walking and the volitional activation task. Additionally, there was a strong positive correlation between peak dorsiflexion during swing phase and active range of motion during the task performance for both tasks. This may provide further evidence of the importance of CST descending drive, a shared mechanism across tasks, for control of the dorsiflexors during walking (Capaday et al., 1999; Schubert et al., 1997), which is also impacted by locomotor central pattern generator circuits (Calancie et al., 1994; Minassian et al., 2017). There was only a small effect of LT on plantar-flexor spasticity, as measured by clonus. Although 2 participants who had pathological spasticity at baseline, as determined by at least 4 beats of clonus oscillations (Koelman et al., 1993), did not have clonus after 4 weeks of LT, one person who did not have pathological spasticity at baseline developed clonus after 4 weeks of LT. This could be because our participants in this study had subacute SCI, in which the natural progression of recovery is highly variable (Burns et al., 2012). In summary, although combined LT and TSS did not show persistent effects on dorsiflexion ability in people with SCI, 4 weeks of LT was associated with increased dorsiflexion across tasks. It will be important to determine if factors other than enhanced dorsiflexor activation are responsible for the effects of TSS on improved walking outcomes in

future studies.

CONCLUSIONS

The purpose of my dissertation was to: 1) synthesize what is known about the neurophysiological mechanisms of dorsiflexor control after SCI, 2) utilize neuromodulatory techniques that target those mechanisms to determine their persistent impacts on dorsiflexor control, and 3) assess dorsiflexor control across different tasks to distinguish the role of these neurophysiological mechanisms in those tasks in persons with SCI. Based on the results of my dissertation, I have established that: 1) a relationship exists between SRC excitability and measures of both volitional ankle control and spasticity, and a relationship between CST descending drive and volitional ankle control, but more work is needed to understand the impact of this relationship on spasticity; 2) noninvasive afferent input in the form of WBV and TSS may not have a persistent impact on dorsiflexor control during walking or volitional activation, but LT may have a persistent impact on these outcomes; and 3) CST descending drive is important for dorsiflexor activation during walking in persons with SCI. Although more work is needed to understand the timing of the effects of neuromodulatory interventions on dorsiflexor control or if other joints involved in walking are more impacted by the techniques utilized, the knowledge gathered in this dissertation is an important step toward the optimization of rehabilitative therapy in persons with diminished ankle control after SCI and other populations, including people with stroke and cerebral palsy, that are impacted by foot drop.

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Appendix I: List of Abbreviations

AIS	ASIA impairment scale
AROM	Active range of motion
ASIA	American spinal injury association
Cl^-	Chloride
CST	Corticospinal tract
DF	Dorsiflexors
EMG	Electromyography
GABA	Gamma aminobutyric acid
H-reflex	Hoffman reflex
IMU	Inertial measurement unit
KCC2	Potassium-Chloride cotransporter 2
LFD	Low frequency depression
LT	Locomotor training
MEP	Motor evoked potential
PF	Plantar-flexor
RMS	Root mean square
SCATS	Spinal cord injury assessment tool for spastic reflexes
SCI	Spinal cord injury
SRC	Spinal reflex circuit
TMS	Transcranial magnetic stimulation
TSS	Transcutaneous spinal stimulation
VAC	Volitional ankle control
WBV	Whole body vibration